Prevalence and Predictors of HIV Infection among Under Five-Year Children Born to HIV Positive Mothers in Muheza District, North-Eastern Tanzania

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ABSTRACT

Background: Human Immunodeficiency Virus (HIV) pandemic has become a serious public health concern worldwide. The prevalence of paediatric HIV infection is largely unknown in many countries in Sub-Saharan Africa (SSA). We aimed to determine the prevalence and predictors of HIV infection among under-5 years children in Muheza District, Tanzania.
Methods: A facility-based study among mothers/guardians with their under-5 years children exposed to HIV infection was conducted from June 2015 to June 2016. Information on HIV status, socio-demographic and other family characteristics was collected using a structured questionnaire. Data analysis was performed using STATA version 13.0.
Results: A total of 576 HIV-exposed under-5 years children were recruited together with their respective mothers/guardians. The HIV prevalence among under-5 years children was 10.6% (95% CI: 8.1-13.1%). The burden of HIV infection was observed among older children aged 25 to 59 months (AOR= 8.0, 95% CI 2.5-26.0) than in the younger children. There was a four-fold (AOR=3.9, 95% CI 1.7-9.1) risk of HIV infection among children born to mothers of unknown HIV status at conception than among children born to mothers with known HIV status. The odds of HIV infection were higher among children who were delivered from home (AOR=2.6, 95% CI 1.0-6.5), received mixed feeding (AOR=2.4, 95% CI 1.2-4.9), and those living far from a health facility (AOR=3.0, 95% CI 1.4-6.5).
Conclusion: The prevalence of HIV among under-5 years children in Muheza is higher among older children. The high prevalence is associated with being born to mothers with unknown HIV status at conception, received mixed feeding, home delivery, and living far from the health facility. Campaigns that provide health educational massages addressing risk factors of HIV need to be emphasised in order to promote the control and prevention of HIV among children.

INTRODUCTION

The HIV pandemic has become a major global public health concern.[1] An estimated 1.7 million children worldwide were infected with HIV by the end of 2020. In the same year, approximately 150,000 new HIV infections occurred in children worldwide with more than 90% of the infections residing in Sub-Saharan Africa (SSA).[2] Tanzania is among the top ten countries in the world worst affected by HIV. In 2016, out of the total number of people living with HIV in Tanzania, 18% of these infections were due to Mother-To-Child Transmission (MTCT).[3] Due to increased accessibility to cost-effective Prevention of Mother To Child Transmission (PMTCT) interventions in Tanzania, the number of children born with HIV had decreased from 26,900 in 2009 to 10,000 in 2016.[2,3] The prevalence of paediatric HIV in SSA varies from country to country.

In Nigeria, a prevalence of 5.3% was reported among healthy children presenting at immunisation clinics.[4] A similarly lower prevalence (3.1%) has also been reported among children with unknown HIV status in Cameroon.[5] In Mali, a prevalence of 10.1% among HIV exposed children aged 18 months and below presented at paediatric clinics was reported.[6]

A hospital-based study in Kenya among HIV exposed infants aged below 12 months found a higher prevalence of 11- 41%.[7] A similar higher prevalence (25%) has been reported among hospitalised children aged above 18 months in Zambia.[8] The strategy of testing all children presenting at health facilities to know their HIV status is very important for providing immediate and appropriate care to those found being HIV infected. However, the World Health Organization (WHO), recommends provider-initiated HIV testing and counselling for all infants and young

children presented at health facilities irrespective of HIV epidemic settings.[9] In addition, Early Infant Diagnosis (EID) of HIV provides an opportunity for HIV exposed infants to receive virological testing between the age of 4 to 6 weeks or at the earliest opportunity thereafter, and those found infected to start on Antiretroviral Therapy (ART) as soon as possible.[9]

Mother-to-child transmission, either during pregnancy, childbirth, or breastfeeding is the most (15 to 45%) predominant source of HIV infection in young children.[10] Maternal immunological status and biological factors have been pointed to increase the risk of MTCT as are the ones through which the underlying socioeconomic and proximate factors operate to exert an impact on child health.[11,12] The risk of MTCT is high in children born with low birth weight or born before 34 gestation weeks. Although the mechanism of MTCT in these low birth weight neonates is unclear, this could reflect prematurity due to inadequate passive or active immunity at that age, combined with significant transmission during labour or delivery.[13,14]

The risk is higher in vaginal deliveries than in caesarean section due to direct contact between infant and HIV-infected maternal body fluids (blood, vagina, and cervical secretions).[15,16] The presence of Sexually Transmitted Diseases (STDs) like gonorrhoea, chlamydiosis, trichomoniasis, or genital infections during pregnancy have been shown to increase HIV transmission.[13] There are pieces of evidence that mothers presenting with malaria during pregnancy have an increased risk of MTCT.[17,18] Several factors that increase the risk of MTCT do exist. However, studies on the determinants of HIV infection among children have focused primarily on maternal viral load.[19]

It has been pointed out that the risk is strongly associated with high maternal viral load and advanced stage of maternal HIV infection during labour and at delivery.[14] High maternal viral load and low Cluster of Differentiation 4 (CD4) count are highly associated with an increased risk of HIV infection in children.[20,21,22] Studies have shown that maternal CD4 cell count of less than 200 cells per mm[3] near delivery and those who have been diagnosed with the severe clinical disease are more likely to transmit the virus than those who are less severely affected by HIV infection.[14,23]

Studies have shown that breastfeeding duration, as well as maternal immune status, are the major determinants of increased risk of MTCT of HIV.[24] The risk of HIV transmission increases drastically among mixed-fed children especially if breastfeeding is mixed with solids during the first 2 months of life and the risk is even more if breastfeeding duration is continued for more than 4 months.[25] The use of Antiretroviral (ARV) drugs by HIV-infected mothers and infant ARV prophylaxis has been shown to reduce the risk of postnatal HIV transmission through breastfeeding.[26,27,28]

Since its inception in 2000, the PMTCT program has made several advancements in most settings including here in Tanzania. In 2010, the WHO recommended Option A regimen. This involved the use of Zidovudine (AZT) from 14 weeks of pregnancy until 7 days post-delivery and infant Nevirapine (NVP) from birth until one week after

cessation of breastfeeding.[29] Later, these guidelines were updated, and Option B regimen was introduced which involved triple ART during pregnancy from 14 weeks of pregnancy until the end of breastfeeding and infant NVP daily from birth up to age 4 to 6 weeks. This regimen was further modified to involve initiating triple ART for life during pregnancy and breastfeeding women irrespective of clinical stage of disease or CD4 count and infant NVP up to the age of 4 to 6 weeks. The regimen was named PMTCT Option B+ and is the best recommended regimen that is currently in use in most settings.[29]

In Tanzania, Option B+ was adopted in 2013, available in a fixed dose combination regimen of one pill taken once per day.[30] However, the current introduction of the Dolutegravir (DTG)-based ART regimen in most settings including Tanzania has dramatically shown to reduce the risks of transmission of HIV, though its safety and efficacy are still under development.[30,31,32] In addition, the use of Cotrimoxazole Preventive Therapy (CPT) among pregnant women with CD4 cell count ≤350 cells/mm^{3} has been shown to reduce the risk of HIV transmission to the child.[30]

Data on the prevalence and predictors of HIV infection in children below 5 years born to HIV positive mothers presenting at health facilities in Muheza, Tanzania is largely unknown. Without knowing the predictors and the burden of HIV among HIV exposed children below 5 years, the policy will not be informed, and as a consequence interventions will not be focused effectively. Therefore, continuous understanding of the contributing factors associated with the epidemiology of paediatric HIV may reveal opportunities to reduce the risk of MTCT of HIV.

The main context of the study is mainly to understand the progress made with the PMTCT intervention in Muheza District, Tanzania, in relation to the risk of MTCT of HIV among exposed under-5 years children. Continuous epidemiological surveys are crucial in this paediatric population, as they will help to know how interventions are working and keep track of the progress and utilize lessons learned for modification of intervention measures and/or development of new interventions. Hence this study aimed to determine the prevalence and predictors of HIV infection among exposed children below 5 years in Muheza, Tanzania.

MATERIALS AND METHODS
Study Area, Design and Population
A facility-based study was conducted in Muheza district in north-eastern Tanzania (4^0, 45'S; 39^000'E) from June 2015 to June 2016. The health care system of Muheza district is comprised of 46 health facilities which includes; one hospital, 4 health centres, and 41 dispensaries of which 36 offer PMTCT services and 28 offer EID services.[33] Study population involved HIV exposed under five-year children and their respective mothers/guardians. A guardian in this study was defined as the child's main primary caregiver living with the child in the same household.

This included either the child's biological parent, grandparent, sister, brother, aunt or uncle. The inclusion criteria were based on the following characteristics:

Mother/guardian who agreed to participate and with an under five-year child born to HIV positive mother (maternal HIV status was confirmed from the district HIV database); under five-year child with a confirmed HIV positive test result. A mother/guardian with HIV exposed under five-year child who was not permanent residents of Muheza district were excluded from this study.

Sampling and Sample Size Determination

The participants were selected by employing a multistage sampling approach. The initial step involved the selection of the district purposively. Muheza district was chosen because it is among the leading district with high HIV prevalence among pregnant women in Tanga Region.[34] Next, a list of health facilities (N=46) was obtained from the district according to their geographical position. Health facilities (clusters) serve as Primary Sampling Units. These health facilities were listed by name and numbered from 1 to 46. Finally, the sampling interval was obtained. From the list, we randomly selected 18 health facilities that provide PMTCT and EID services. Before initiation of data collection, a list of HIV exposed under five-year children was obtained from the registers/database at each health facility. The list was numbered and all eligible under five-year children each with their respective mother/guardian were selected randomly using the lottery method and enrolled based on the inclusion criteria. The sample size (n) was calculated based on the formula that accounted for simple random sampling and the design effect, where by $n = z^2 p (1-p)*DEFF/d^2$.[35]

The Design Effect (DEFF) was adjusted by a factor of 2, at a 95% Confidence Interval (CI) with a Z value of 1.96, and the desired level of absolute precision (d) was taken at 5%. The transmission rates of HIV from mother to child range between 20 and 45%.[36] The highest exposure of infection risk (p) was taken at 45% and a response rate of 90%. Hence the estimated sample size $[(1.96)^2*45(100-45)*2/5^2]$ was 760 + 76 = 836 under-five year children. However, the minimum and maximum numbers of mother/guardian-child pairs in each cluster was set at 20 and 50 respectively. But, the proportion to size was employed based on the estimated total number of HIV-exposed under five-year children at a particular health facility. In this study a total of 576 mother/guardian-child pairs were enrolled. More details of this study have been described elsewhere.[37]

Data Collection

Socio-demographic factors of the mother/guardian-child pair (age, sex, residence, marital status, occupation, knowledge of HIV and distance from a health facility (which was defined by time taken in minutes to reach the health facility on foot) were collected using a structured questionnaire. Mother/guardian's knowledge on HIV was assessed based on 4 key questions that addressed general MTCT knowledge; prevention of MTCT; timing of post-exposure prophylaxis to HIV exposed infant and factors affecting HIV transmission. Maternal information which included CD4 cell count levels during pregnancy, HIV status before conception and history of taking CPT during pregnancy was also collected. The child's HIV status was extracted from the HIV database available at the district hospital. In addition, during recruitment, more data on children and their biological mothers were extracted from registers, HIV database, hospital case files for children under five-year or antenatal cards, and PMTCT records to supplement the collected primary data.

Data Management and Analysis

All data were double entered in Epi Data database version 3.1 by two separate data clerks. Data were compared directly at entry with a previous entry of the same data. After finishing data entry, data were validated in Epidata, and any discrepancy observed was clarified by editing the data and comparing it with original data forms, and redoing the validation. The amount of discrepancy allowed was 2%. The validation process continued until all data were compared. After validation of data was completed, data were exported to STATA version 13 (Stata Corp, College Station, Texas, USA) for analysis. The analyzed data was validated by the Minitab version 19 statistical software and the results were comparable. Data were summarised using descriptive statistics and graphical summary, whereby, continuous variables were described using median and Inter-Quartile Range (IQR).

Categorical variables were described using frequencies and percentages. The child's HIV status was categorised into a binary variable; 'HIV positive or HIV negative'. A composite variable on knowledge on HIV was developed based on 4 key questions by the use of recoding and computing commands to form a single unit composite variable with a binary outcome 'good' or 'poor'. The 4 variables composition for good knowledge comprised of; 1) MTCT can occur and can be prevented, 2) MTCT can be prevented by taking ARV drugs during pregnancy, 3) HIV can be transmitted in utero, during delivery, and through breastfeeding, 4) post-exposure prophylaxis to HIV exposed infant should be given soon after birth within 6 to 12 hours post delivery. The 4 variables composition for poor knowledge comprised of 1) MTCT can occur and can be prevented, 2) MTCT can be prevented by taking fansidar (*Sulphadoxine Pyrimethamine*), ferrous and traditional medicines during pregnancy, 3) HIV can be transmitted by mosquito bites, evil spirits and by sharing food with a person who has AIDS, 4) did not know the correct timing of post-exposure prophylaxis to HIV exposed infant. The development of a composite variable for good or poor knowledge of HIV comprised of all the 4 data sets as described above.

All variables from univariate analysis with P values of ≤0.2 were fitted to the multivariable logistic model. Multiple logistic regression analyses were used to examine the associations between various socio-demographic factors of the mother/guardian-child pairs and the child's HIV infection status. A stepwise Logistic Regression was employed by removing variables that were statistically non-significant at *P- value* of ≤ *.05*. The final modal comprised of variables with Adjusted Odd Ratios at 95% Confidence Interval (CI) which was taken as significant predictors for HIV infection in under five-year children. Crude Odds Ratios (COR) with corresponding *P-values* were also presented.

Ethical Considerations

Ethical approval was obtained from the Medical Research Coordinating Committee of the National Institute for Medical Research in Tanzania with reference number: -

NIMR/HQ/R.8a/Vol. IX/1978. Permission to conduct this study was given by Muheza District Council Authority. Written informed consent was obtained from each mother/guardian before the recruitment of study participants. All participants were identified by numbers throughout the study. No names were used to identify participants during data collection, report, or publication of study findings

RESULTS
Socio-Demographic characteristics of Study Populations
A total of 576 mothers or guardians each with HIV exposed under five-year child were involved. Out of 576 under five-year children, 281 (48.8%) were males and 295 (51.2%) were females. The majority 528 (91.7%) of under-five children were delivered at health facilities and 48 (8.3%) at home. Out of 576 children, 251 (43.6%) were born to mothers with unknown HIV status at conception. A total of 433 (75.1%) of the under-five year children received exclusive breastfeeding, 130 (22.6%) received mixed feeding and 13 (2.3%) received replacement feeding. A total of 83 (14.4%) children did not receive NVP prophylaxis at birth and the period thereafter. Out of 576 mothers/guardians, 549 (95.3%) were the biological mothers of the respective children. Slightly more than half of the mother/guardian child pair had to walk for more than 30 minutes to the nearest health facility.

HIV Prevalence among Children
Out of 576 under-five year children, 61 were confirmed to be HIV positive. The HIV prevalence was reported to be 10.6% (95% CI: 8.1-13.1%) A total of 46 (75.4%) HIV-positive under five-year children were diagnosed at ≥ 12 months old. Among 61 HIV-positive under-five year children, 52 (85.2%) reported receiving their first HIV testing at more than 6 weeks of age (Figure 1). The Median age at diagnosis among those confirmed to be HIV positive was 20 months (IQR: 12.5-35 months). Accordingly, 4 (6.6%), 12 (19.7%), and 45 (73.7%) HIV-positive under five-year children were in the ≤ 11 months, 12 to 23 months, and 24 to 59 months age group respectively (Figure 1).

Predictors of HIV Infection in Children
In multiple logistic regression model, children who were older, delivered at home, born with low birth weight, received mixed feeding practices, born to mothers with unknown HIV status at conception, born to mothers with known HIV status at conception with the absence of CPT during pregnancy and lived far from the health facility were significantly and independently associated with HIV infection (Table 1).

Higher odds of HIV infection were observed among older children aged 25 to 39 months (AOR= 8.0, 95% CI 2.5-26.0) than in younger children. The risk of HIV infection was 2.6 (AOR=2.6, 95% CI 1.0-6.5) times higher among children delivered at home than among those delivered at a health facility. Children born with low birth weight of < 2500g had a 3.4 (AOR=3.4, 95% CI 1.2-9.3) times higher risk of HIV infection compared to those born with ≥ 2500g. The risk of HIV infection in children was 2.4 (AOR=2.4, 95% CI 1.2-4.9) times higher among those who received mixed feeding compared to those who wer-

e exclusively breastfed. There was a 4-fold (AOR=3.9, 95% CI 1.7-9.1) risk of HIV infection among children born to mothers with unknown HIV status at conception compared to those born to mothers with known status. There was a 3-fold (AOR=2.7, 95% CI 1.1-7.2) risk of HIV infection among children born to mothers with known HIV status at conception with the absence of CPT compared to those with the presence of CPT during pregnancy. The risk of HIV infection was 3.0 (AOR=3.0, 95% CI 1.4-6.5) times higher among those who lived far from a health facility as compared to those living close to a health facility (Table 1).

FIGURE 1. Proportion of HV positive under five-year children according to age at HIV diagnosis and access to first HIV testing in Muheza district, Tanzania
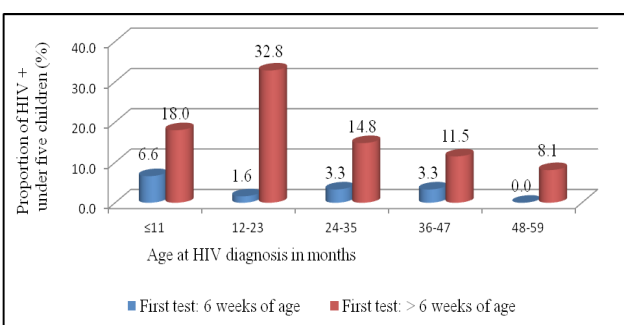
The odds of infection were reduced among children who had received NVP after delivery (AOR=0.3, 95% CI 0.1-0.5) compared to non-recipient of *Nevirapine*. Similarly, the odds of infection were reduced among children born to mothers with a CD4 cell count of ≥ 350 cell/µl (AOR=0.3, 95% CI 0.1-0.8) compared to those with low CD4 cell count (Table 1). The Guardian's marital status, occupation, knowledge of HIV, and residence did not show any association with the child's HIV infection.

DISCUSSION
Results from this study indicate that nearly 3 quarters of under- five-year children diagnosed with HIV infection in Muheza district, the diagnosis was done at more than one year of age. The majority of HIV-positive children were in the age group, between 13 to 59 months and accessed their first HIV testing at more than 6 weeks of age. Studies from Ethiopia and Tanzania reported that HIV transmission was higher in infants enrolled late than in those who were presented earlier.[39,40]

This suggests that late HIV testing in children at older ages may be triggered by symptoms that make their parents/guardians bring them to the health facility for diagnostic testing. Children born to mothers with unknown HIV status at conception were more at risk than those born to mothers with known HIV status. A study in Mozambique reported that EID programs target infants born to mothers with known HIV-positive status.[41] This implies that most of the HIV-infected children will not be identified if EID services are offered only to children born to mothers with

TABLE 1: Predictors of HIV infection among under five-year children in Muheza district, Tanzania

Child and maternal variables	n (%)	OR (95% CI)	
		Unadjusted	Adjusted
Child age (months)			
≤ 12	224 (38.8)	1	1
13-24	155 (26.9)	5.9 (1.9-18.1)**	3.7 (1.1-12.7)**
25-59	197 (34.2)	14.9 (5.2-42.4)*	8.0 (2.5-26.0) #
Place of delivery			
Health facility	528 (91.7)	1	1
Home	48 (8.3)	3.7 (1.8-7.5)*	2.6 (1.1-6.5)**
Birth weight			
≥ 2500	525 (91.2)	1	1
< 2500	51 (8.9)	1.6 (0.7-3.7)	3.4 (1.2-9.3)**
Mode of feeding			
Exclusive breastfeeding	433 (75.1)	1	1
Replacement feeding	13 (2.3)1.4	(0.2-10.9)	0.5 (0.1-5.0)
Mixed feeding	130 (22.6)	6.0 (3.4-10.5)*	2.4 (1.2-4.9)**
NVP prophylaxis			
0 day	83 (14.4)	1	1
1-90 days	493 (85.6)	0.08 (0.04-0.14)*	0.3 (0.1-0.5)*
Maternal CD4 cell count			
≤ 349 cell/µl	189 (32.8)	1	1
≥ 350 cell/µl	214 (37.2)	0.3 (0.1-0.6)#	0.3 (0.1-0.8) #
Unknown	173 (30.0)	1.3 (0.7-2.3)	0.9 (0.4-2.0)
Maternal HIV status at conception			
Known	325 (56.4)	1	1
Unknown	251 (43.6)	8.0 (4.0-16.0)*	3.9 (1.7-9.1)#
Maternal known HIV status at conception with			
Presence of CPT during pregnancy	480 (83.3)	1	1
Absence of CPT during pregnancy	(96) 16.7	14.2 (7.9-25.7)*	2.7 (1.1-7.2)**
Distance to the health facility			
Near (≤30 minutes)	267 (46.4)	1	1
Far (>30 minutes)	309 (53.6)	3.2 (1.7-6.0)*	3.0 (1.4- 6.5)#

Notes: (a) Total sample size N=576 (b) CPT=Cotrimoxazole Preventive Therapy; NVP=Nevirapine (c) OR: Odds ratio, CI=Confidence interval (d) P values: #p<.01, * p<.001, ** p<.05

known HIV status.

Similar to our findings, vertical transmission of HIV has been considered to be higher among children delivered at home, living far from health facilities, and among those who received mixed feeding.[39,42] It has been reported that, in mixed-fed children, the risk of HIV transmission is high throughout breastfeeding and the risk is even more if breastfeeding duration is prolonged for more than 4 months.[25] However, children born from rural mothers or hard-to-reach areas are more prone to mixed feeding, the choice that is commonly practiced throughout Africa.[43,44] In this study, place of residence was not a significant risk factor after adjustment with other variables. Recent studies in Tanzania, Rwanda, and Ethiopia reported less HIV transmission among urban children than in rural ones.[39,40,45] This could be due to inefficient PMTCT services or inaccessibility to health facilities in rural areas when compared to urban areas. Most women in low-income countries do not have access to antenatal services and present late with symptoms at health facilities which could affect the health outcome of both the mother and child.[46]

In our study, children who received ARV prophylaxis were found to have a reduced risk of acquiring HIV infection than those who were not taking ARV prophylaxis. The same is reported in studies conducted in Zimbabwe, Kenya, and Ethiopia.[47,48,49] Children born to HIV-positive mothers who did not take CPT during pregnancy had a higher risk of vertical transmission in this study. A study in Ethiopia and elsewhere in Tanzania also found that la-

ck of maternal PMTCT interventions was significantly associated with MTCT of HIV.[39,50] It was observed in this study that children born to mothers with a high CD4 cell count of more than 350 cells/µl were at reduced risk of being infected. The risk of MTCT of HIV has been reported among mothers with advanced disease who presented with low CD4 counts in several studies.[53,54,55,56]

The risk of HIV transmission from mother to child was observed in mothers with CD4 cell count of less than 200 cells/mm3 despite the use of maternal ARV treatment.[3,51,52] Low birth weight has been associated with advanced maternal HIV status in studies conducted elsewhere in Tanzania and Côte d'Ivoire. [56,57] This is consistent with this study's findings.

Limitations
The study could not establish temporal or causal relationships between exposure and outcome, the study only describes associations. Selection bias, since sample population selection only considered those who attended health facilities within the district. Mothers and children who were identified within communities through other means were left out, resulting in a sample that is not representative of the whole population in the study area.

The findings could also be affected by a shortfall of 30% of the estimated sample size of the study. The wider 95% confidence interval of the older age group (25 to 59 months) implies that the sample size for this variable was relatively small, and so reducing the precision of the finding for this variable. Information bias, since some mothers/ guardians may not report correctly some information regarding mother-child pair such as the history of taking CPT during pregnancy, the date which the HIV status of the mother was confirmed, or the history of taking infant NVP. However, this was minimised by verifying received information using hospital case files, children under 5 years or antenatal cards, and PMTCT records.

However, while factors included in the multiple variables logistic model were each potentially important factors associated with predictors of HIV infection among under 5 years children, it is difficult to eliminate the probability that the results were influenced by unmeasured confounders.

CONCLUSION
The burden of HIV among under-5 years children in Muheza district is higher among the older age category. The high prevalence is associated with being born to mothers with unknown HIV status at conception, absence of CPT during pregnancy of the index child, absence of infant NVP prophylaxis, mixed feeding of infants, home delivery, and living far from the health facility. This does not only show limitations in testing efforts, but it suggests the need for reshaping the current national HIV testing policies for women and men so that pre-pregnancy HIV status is prioritised. However, the findings underscore the need to focus on improved preventive health care before pregnancy, pre- and post-natal period for mothers and babies in order to reduce the risk of MTCT of HIV in areas with similar settings. Strengthening health and education programmes will have a direct benefit as it increases awareness of their children's needs to prevent them from acquiring infection.Although there has been some development in this area, the available evidence in this study population, the under five-year children is still limited. Hence, these pieces of evidence obtained from this study will save as a reference baseline to compare with other epidemiological surveys that will help to know the efficiency of interventions.

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