



Lost to Follow-up and Predictors Among HIV-Exposed Infants in Northwest Ethiopia

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ABSTRACT

Introduction: Even though advancement in mother-to-child HIV transmission prevention services is observed, many infants are lost to follow-up and could not access the full package of mother-to-child HIV transmission prevention services as a result. This is one of the obstacles to the effectiveness of the program. Therefore, determining the magnitude of lost to follow-up and its predictors is important among HIV-exposed infants.

Method: This institution-based retrospective cohort study was conducted from August 2013 to June 2018 at the University of Gondar Comprehensive Specialized Hospital. We

retrieved charts of 423 child–mother pairs through a simple random sampling technique. Data collectors extracted data by using a data extraction tool adapted from the Ethiopian Federal Ministry of Health HIV-exposed infant follow-up form. Bivariable and multivariable Cox regression models were fitted to identify predictors of lost to follow-up.

Result: A total of 402 child–mother pairs were included in the study. Of the study participants, 6.0% were lost to follow-up for more than 3 months before the declaration of their HIV status. Born from rural residence mother (AHR = 3.5; 95% CI 1.549–7.894), infants whose mothers have three and more children (AHR = 3; 95% CI 1.284–6.963), and low birth weight infants (AHR = 3.2; 95% CI 1.055–9.450) were independent predictors of lost to follow-up among HIV-exposed infants.

Conclusion: Significant numbers of infants were unable to access full HIV diagnosis and care services as a result of loss to follow-up. Special consideration for mothers having large numbers of children, rural residence, and low birth weight infants could be an important intervention to decrease lost to follow-up.

Keywords: Ethiopia; HIV-exposed infant; Lost to follow-up; Predictors

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Key Summary Points

Why carry out this study?

HIV-exposed infants are a vulnerable population for HIV infection and related complications as they need special care and support.

Lost to follow-up from service is one of the challenges to accessing the full package of mother-to-child HIV transmission prevention services for this vulnerable population.

This study tries to show the magnitude of lost to follow-up and contributing factors among HIV-exposed infants in relation to mother-to-child HIV transmission prevention services.

What was learned from the study?

A number of infants were unable to access full HIV diagnosis and care service as a result of lost to follow-up in health care services.

Infants born into a large family, from a rural residence, and with low birth weight were more prone to be lost from HIV care and support services.

Therefore, those infants who are at risk for lost to follow-up need special attention to retain them in the health care services.

DIGITAL FEATURES

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INTRODUCTION

It has been estimated that globally around 37.9 million people were living with human immunodeficiency virus (HIV) in 2018, and of these more than 23 million were receiving antiretroviral therapy (ART) [1]. In 2013, about 3.2 million children below the age of 15 years were living with HIV worldwide, 91% of them in sub-Saharan Africa [2]. In sub-Saharan Africa numerous HIV-infected infants and children died of HIV-related illnesses without knowing their HIV status. In the first one and a half years of life, nearly one-third of infants died because of poor access and utilization of ART, supportive care, and prophylactic drug treatments [3]. One of the prevention of mother-to-child transmission (PMTCT) interventions, early infant diagnosis (EID), has aimed to identify HIV-infected infants before the occurrence of clinical disease to enhance care and follow-up [4]. Lost to follow-up (LTFU) of HIV-infected and exposed individuals remains the major obstacle to the efficacious delivery of HIV care and support programs in sub-Saharan Africa [5].

In the absence of protective measures, the possibility of acquiring HIV during pregnancy and delivery is 15–30%, and the risk will be raised to 20–45% with breastfeeding. The PMTCT schemes can minimize the vertical transmission of HIV to less than 1% in advanced nations; however, in spite of its positive progress, the success rate is poor in developing countries [6, 7]. Although the global rate of transmission of HIV reduced from 26% in 2009 to 10% in 2015, PMTCT remains a challenge for HIV control strategy [8].

In a public-funded urban hospital in Johannesburg, South Africa, almost half of the infants born to HIV-infected mothers in a routine PMTCT service were lost to follow-up by 2 weeks of age [9].

In spite of the development of knowledge of effective interventions to save the lives of HIV-exposed infants, several exposed infants do not get the full package of amenities due to LTFU [10].

In Africa several studies have verified the huge number LTFU rate of children with an

interval of 36.9% and 68.4%; such unacceptably high LTFU prevalence experienced by PMTCT programs impedes the provision of appropriate interventions for HIV-infected children. This resulted in the poor success of PMTCT and is one of the main explanations for why more than 90% of the children who acquired HIV infection in 2011 live in sub-Saharan Africa [11].

In Malawi, the loss to follow-up rate of patients receiving HIV care and treatment has been unacceptably high. In 2012, about 100,624 patients (18%) were lost to follow-up and therefore missed the opportunity of benefiting from ART care and support [12]. Other studies also reported that in Cameroon 47.37% and in Uganda 48% of infants were lost to follow-up [13, 14].

A study in Kenya reported that 22% of infants were LTFU at 18 months of age [15].

In Ethiopia, only 40% of HIV-positive pregnant women and less than a quarter of newborns of these women received ART prophylaxis. On the other hand about 11% of exposed infants received virologic investigation for HIV within 6 weeks of birth [16].

Several social, cultural, economic, and infrastructural factors contribute to the poor outcomes of PMTCT and a higher rate of LTFU. These factors are composite, with some involving the children themselves, the caregivers, the family structure and society, and the health care systems. There may not be single factors that appear to be replicated across the board because of differences in culture and approaches by various HIV programs across Africa. Some of the factors that have been linked to LTFU are discussed below. A study conducted in India showed that poor educational status, lower wealth quintile, and being registered after 20 weeks of gestation of pregnancy were predicting variables affecting LTFU [11]. A hospital-based case-control study in Cameroon indicated that mothers who had no formal education were more likely to be lost to follow-up with HIV care programs compared to those who attended formal education [17].

Knowledge of the factors associated with LTFU has potential utility in deciding for patient retention in pediatric HIV care programs. Further, knowing the factors leading to

LTFU may provide unique opportunities for early intervention, to augment retention in HIV programs and improve overall outcomes of these children. But the magnitude of and factors associated with loss to follow-up of HIV-exposed infants are not yet investigated well in Ethiopia. Therefore, the main objective of this study was to determine the magnitude of and identify factors associated with loss to follow-up among HIV-exposed infants.

METHODS

Study Setting

The University of Gondar Comprehensive Specialized Hospital is expected to serve more than five million people from different parts of the country. Since 2005 the hospital has started providing HIV care and support including ART for children and adults, and PMTCT services for mothers and their children. After 2013 the hospital has started “option B+”—the new PMTCT approach for the mother and childcare as recommended by the Ethiopian Federal Ministry of Health. According to the Ethiopian Ministry of Health’s national PMTCT guideline, all HIV-exposed infants must enroll in follow-up and care soon after delivery, and at 6 weeks PCR/DNA (polymerase chain reaction /deoxyribonucleic acid) analysis is conducted. ART initiation is determined on the basis of the result of the test [18]. If HIV negative, follow-up is continued up to 18 months until HIV negative is reconfirmed. Infants are expected to be discharged from the follow-up after the HIV rapid antibody test done at 18 months or after a 6-week cessation of breastfeeding.

Study Design and Period

A hospital-based retrospective cohort study was conducted from August 2013 to June 2018 in the University of Gondar Comprehensive Specialized Hospital, Northwest Ethiopia and the data were extracted from February to March 2019.

Study Population

The study population comprised all mothers and children who were registered for HIV care between August 2013 and June 2018 at the University of Gondar Comprehensive Specialized Hospital, Northwest Ethiopia.

Inclusion and Exclusion Criteria

All children and mothers who have complete baseline registration were included in this study. (Baseline data comprised the sex, birth weight, and gestational age at birth of the infants and the age, ART starting time, baseline CD4 count, and baseline WHO clinical stage of the mothers.)

Sampling Technique and Procedures

The sample was determined by using a single population proportion formula and double proportion by using common factors from a previous study [9]. The largest sample size was 423 calculated from a single population proportion. The participants of this study were selected using simple random sampling technique. First, the total number of exposed children were identified from their registration number with the study. Then, study participants were selected using a computer-generated random number. After identifying the infant unique registration number, the mother unique registration numbers were accessed. Finally, all the necessary data variables were collected manually in the follow-up program.

Operational Definitions

HIV-exposed infant	Infant born from HIV-positive mothers
Lost to follow-up	Infants missing their appointment for more than 3 months
Censored	Infants who transfer out, completed follow-up, attending follow-up according to schedule, and dead were considered as censored

Data Collection Tools

Data were extracted by using data the extraction tool customized from the Ethiopian Federal Ministry of Health's HIV-exposed infant follow-up chart. Data were collected from the charts and registration books of HIV-exposed infant–mother pairs.

Data Quality Control Measures

The data extraction tool was checked before the actual data collection period to ensure that data from the chart and follow-up registration book matched the information in the document and the data collection tool, and modification was made accordingly. Three PMTCT trained nurses were recruited for data collection. The data collection process was closely monitored by one MSc nurse supervisor on a daily basis to ensure the quality of data. One day of training was given to data collectors and the supervisor on objectives of the study, data collection tool, procedure, and ethical issues. Sociodemographic characteristics of mother–infant pairs, pregnancy, delivery, and clinical-related characteristics of mothers, and proportion of infants lost to follow-up were collected through the paper-based data collection tool.

Data Processing and Analysis

Data were collected first using the paper-based tool and then after collection the data were entered and coded using EPI Info version 7. Then, data were exported to SPSS version 20 for further analysis. The sociodemographic characteristics and proportion of lost to follow-up were described through descriptive statistics. Bivariable and multivariable Cox proportional hazard regression models were used to identify predictors of lost to follow-up. Variables with p value ≤ 0.2 in the bivariable analysis were fitted into the multivariable model. The Cox proportional hazard model assumption was checked by using the Schoenfeld residuals test. The adjusted hazard ratio (AHR) with a 95% confidence interval (CI) was calculated. p value

≤ 0.05 was considered as statistically significant.

Ethical Considerations

This study was conducted in compliance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The Institutional Review Board of Gondar approved this study. A permission and support letter was obtained from University of Gondar Comprehensive Specialized Hospital's chief clinical director after ethical approval and it was distributed to concerned offices. Since we used secondary data, it was impossible to get consent from mothers, and as result consent has been waived. Confidentiality of the information was maintained in hard and soft copy by locking and using a password as appropriate.

RESULTS

Sociodemographic Characteristics of Mothers

A total of 402 mother–child pairs were included in this study, which is 95% of the total sample size. Most of the mothers (81.6%) were from urban areas and the majority (90%) were Orthodox Christian religion followers. Nearly three-quarters (76.9%) had attended at least primary education. Regarding the marital status of the mother, 72.1% were married. More than of half mothers (61.7%) were between the ages of 19 and 30 years (Table 1).

Sociodemographic and Health-Related Characteristics of HIV-Exposed Infants

Of the 408 HIV-exposed infants included in the study, nearly half (51.7%) were male. Almost all (99.5%) of the HIV-exposed infants had good adherence to cotrimoxazole preventive therapy, which means the probability of missing a dose is 3 or less per month. Ninety-eight percent of the infants had taken daily prophylactic nevirapine for 6 weeks. Regarding birth weight, 66.2% had normal birth weight and 90.5% were term gestational age at birth. In the first

Table 1 Sociodemographic characteristics of mothers in University of Gondar comprehensive specialized hospital ($n = 402$)

Characteristics	Number	Percent (%)
Maternal age		
< 25 years	70	17.4
25–30 years	178	44.3
30–35 years	86	21.4
≥ 35 years	68	16.9
Marital status of mother		
Married	290	72.1
Unmarried ^a	112	27.9
Religion of mother		
Orthodox Christian	362	90.0
Muslim	30	7.4
Protestant	10	2.6
Residence of mother		
Urban	328	81.6
Rural	74	18.4
Occupation of mother		
Government employed	107	26.6
Non-governmental employed	133	33.1
Housewife	162	40.3
Educational status of mother		
No formal education	93	23.1
Primary education	136	33.8
Secondary education	113	28.1
College and above	60	14.9
Number of births		
≤ 2	258	64.2
≥ 3	144	35.8

^a Unmarried (single, widowed, divorced, separated)

6 months, most (95.5%) of the infants were on exclusive breastfeeding and most of their parents (92.5%) were alive.

Table 2 Pregnancy, delivery, and clinical-related characteristics of mothers in University of Gondar comprehensive specialized hospital ($n = 402$)

Characteristics	Number	Percent (%)
ANC visit		
No ANC	23	5.7
First visit	16	4.0
Second visit	52	12.9
Third visit	49	12.2
Fourth visit	188	46.8
Fifth visit	74	18.4
Place of delivery		
Hospital	358	89.1
Health center	44	10.9
Mode of delivery		
SVD	347	86.3
CS	55	13.7
ART starting time		
Before pregnancy	230	57.2
During pregnancy	161	40.0
After labor	11	2.7
Infant feeding practice in the first 6 months		
EBF	384	95.5
Non-EBF	18	4.5

ANC antenatal care, EBF exclusive breastfeeding, SVD spontaneous vaginal delivery, CS caesarean section, ART antiretroviral therapy

Pregnancy, Delivery, and Clinical-Related Characteristics of Mothers

From the reviewed maternal charts, the majority (94.8%) of the mother had attended at least one antenatal care (ANC) and more than half (57.2%) of the mothers had started ART before this pregnancy (Table 2).

Magnitude of Lost to Follow-up Among HIV-Exposed Infants

Out of 402, HIV-exposed infants, 24 (6.0%) infants were lost to follow-up for more than

3 months before the final HIV status was determined. The infants were followed for a minimum of 3 months and a maximum 20 months with a median of 13 months of age. Nearly all (93.8%) of the infants had enrolled in an HIV-exposed infant follow-up program within the first 6 weeks of life. Most (79.2%) of the infants were lost to follow-up before their first birthday (Fig. 1).

Predictors of Lost to Follow-up

From the bivariable Cox regression analysis, residence of the mothers, number of births, educational status of the mothers, birth weight of the infant, and marital status of the mothers were associated with lost to follow-up among HIV-exposed infants. In the multivariable regression model, residence of the mothers, number of births, and birth weight of infants were independent predictors of lost to follow-up. Infants whose mothers live in rural areas were at 3.5 (95% CI 1.549–7.894) times higher risk of lost to follow-up compared with infants whose mothers live in urban areas. Infants whose mothers have three or more children were at 3 (95% CI 1.284–6.963) times higher risk for lost to follow-up. Infants whose birth weight was less than 2.5 kg were at 3.2 (95% CI 1.055–9.450) times higher risk of lost to follow-up compared with infants whose weight is 2.5 kg or above (Table 3).

DISCUSSION

This study revealed that 6% (95% CI 3.7–8.2) of HIV-exposed infants were lost from HIV care follow-up. This implies that 6% of infants did not return for PMTCT services for at least 3 months before their final HIV status was declared. The finding is lower than studies conducted in Angola (19.3%) [19], Cameroon (18%) [20], Amhara region, Ethiopia (34%) [21], Addis Ababa, Ethiopia (30.5%) [22], Malawi (48%) [23], Central Mozambique (50%) [24], South region of Nigeria (67%) [25], Uganda (43%) [26], Brazil (15.4%) [11], and North India (29%) [27]. A possible reason for this discrepancy may be the difference in definition of lost

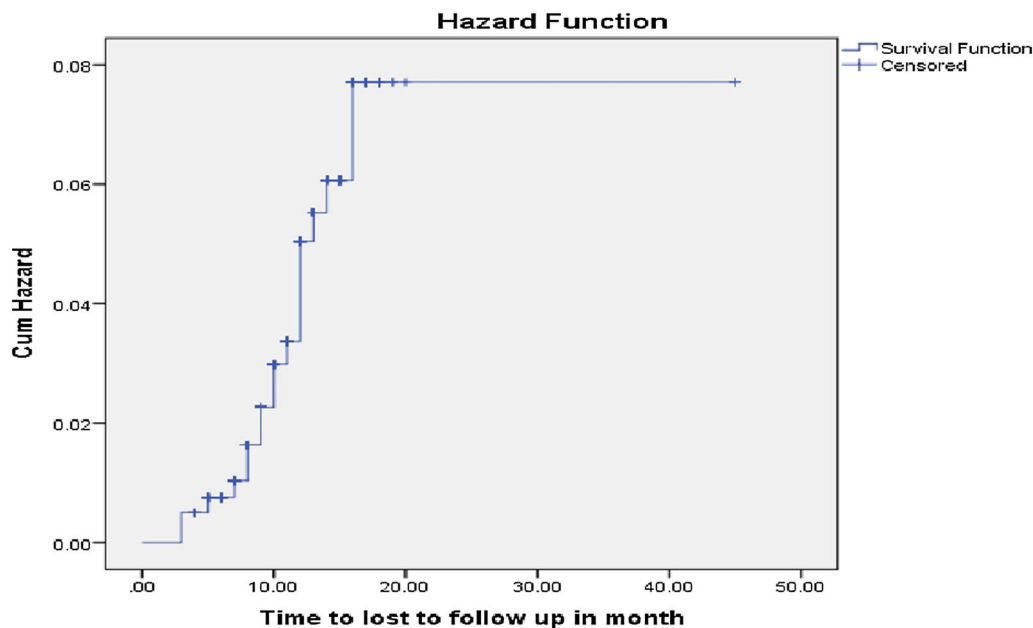


Fig. 1 Kaplan–Meier curve of proportion of lost to follow-up on the *y*-axis and time to lost to follow-up on the *x*-axis among HIV-exposed infants

to follow-up: in Brazil lost to follow-up was declared as absent from one schedule visit for PMTCT service and in Malawi missing from appointments for 2 months, but in this study lost to follow-up was defined as absent from PMTCT service for more than 3 months. Another possible explanation for this variation could be the change in intervention, as the aforementioned studies were conducted before the implementation of “option B+”, which is a new PMTCT approach. This approach endorses initiating life-long ART for all pregnant, laboring, and lactating women, improving ART coverage, testing for HIV and starting highly active antiretroviral therapy (HAART) for all HIV-positive children, and early diagnosis for HIV-exposed infants. All this improves health service utilization that reduces the lost to follow-up of mothers and their child. This study also reported different predictors of lost to follow-up. Maternal residence, number of births, and birth weight were independent predictors of infants lost to follow-up. Infants whose mothers were from the rural residence were at 3.5 times higher risk of lost to follow-up as compared with infants whose mothers were from urban areas. This finding is supported by previous

studies conducted in Brazil [11] and Zambezia, Mozambique [28]. Possible reasons for this difference may be due to distance from a health facility [29, 30], inaccessibility of transport [31], poor transport infrastructure [32], economical reasons for transport, and high working burden in the house for mothers [33–35]. Another issue that might affect this service utilization relates to fear of stigma and discrimination, which particularly affects the rural community [31]. Fear of stigma and discrimination could affect people in many ways; it may cause mothers to go far to find a health facility and the might decide to miss frequent visits to the health facility. On the other hand, fear of stigma and discrimination may end up with them not disclosing their status which directly hinders the PMTCT service utilization [36]. Another possible justification for the higher probability of lost to follow-up among rural residence infants might be related to poor access to other infrastructure, like electricity and telecommunication. In Ethiopia, accessibility to electricity and the network is poor, especially in rural areas. Poor electricity even for phone charging, not having a phone, and poor network access make it very challenging for early tracing systems for

Table 3 Bivariable and multivariable Cox regression analysis of predictors of lost to follow-up among HIV-exposed infants in the University of Gondar Comprehensive Specialized Hospital, Northwest Ethiopia

Characteristics	Category	Lost to follow-up	Censored	CHR (95% CI)	AHR (95% CI)
Residence of mother	Urban	13	315	1	1
	Rural	11	63	4.062 (1.650–9.997)	3.497 (1.55–7.894) ^a
Educational status of mother	No formal education	3	90	1	1
	Primary education	7	129	1.517 (0.392–5.867)	1.737 (0.435–6.93)
	Secondary education	5	108	1.393 (0.333–5.831)	2.32 (0.610–8.818)
	College and above	9	51	4.880 (1.32–18.037)	3.45 (0.85–14.04)
Number of births	≤ 2	11	247	1	1
	≥ 3	13	131	2.023 (0.906–4.517)	2.989 (1.28–6.96) ^a
Birth weight of infant	≥ 2.5 kg	18	248	1	1
	< 2.5 kg	6	130	1.467 (0.582–3.699)	3.157 (1.055–9.45) ^a
Marital status of mother	Married	20	270	1	1 ^a
	Unmarried	4	108	1.962 (0.671–5.742)	1.399 (0.517–3.784)

^a The highlighted AHR values are statistically significant

infants lost from their HIV care follow-up [37]. Another maternal-related factor that predicts infants lost to follow-up was having large numbers of children. Those infants from mothers having three and more children were at three times higher risk for lost to follow-up compared with mothers having fewer than three children. This may be because those mothers having large numbers of children may not have adequate time to take their exposed infants to every scheduled follow-up for a longer duration of time. Another possible reason may be that mothers having large numbers of children may be the only care provider for the remaining children in the home; as a result,

it may be challenging for her to take the exposed infant to the health facility [30]. The third predictor for infants with lost to follow-up was being of low birth weight. Those infants weighing less than 2.5 kg were at 3.2 times higher risk for lost to follow-up than infants weighing 2.5 kg and above. A possible reason for this may be that low birth weight infants may have more frequent illness than those with normal birth weight. This may force mothers to seek recurrent health facility visits in addition to the scheduled follow-up, which creates a double burden for the mothers. Another possible reason may be that those low birth weight infants may suffer from illness and as a result

the mother may visit different religious, cultural, and traditional healers, and this may detach the mother from health care visits. As a result, the infants may be absent from scheduled visits for PMTCT [38, 39].

This study has tried to include data for mother–infant pairs from the hospital starting from the implementation of the new PMTCT approach, which is “option B+”. Therefore, this study suggests that the implementation of “option B+” has shown a promising effect in the reduction of lost to follow-up among HIV-exposed infants. This study has limitations: it involves data from a single hospital and is not multicenter; other limitations are that it could not include the reason for lost to follow-up and tracing was not conducted by investigators.

CONCLUSION

Significant numbers HIV-exposed infants did not attend the full PMTCT package because of loss to follow-up. Special attention should be given for those mothers having large numbers of children and from rural residence; and prevention of occurrence of low birth weight and further treatment early whenever it occurs. Improvement of the tracing system for those mothers from rural and remote areas, mothers having large numbers of children, and low birth weight infants could be a strategy for reduction of loss to follow-up for HIV-exposed infants.

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Compliance with Ethics Guidelines. This study was conducted in compliance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The Institutional Review Board of Gondar approved this study. A permission and support letter was obtained from University of Gondar Comprehensive Specialized Hospital’s chief clinical director after ethical approval and it was distributed to concerned offices. Since we used secondary data, it was impossible to get consent from mothers, and as result consent has been waived. Confidentiality of the information was maintained in hard and soft copy by locking and using a password as appropriate.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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