

# Predictors and impact of losses to follow-up in an HIV-1 perinatal transmission cohort in Malawi

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**Background** Large simple trials which aim to study therapeutic interventions and epidemiological associations of human immunodeficiency virus (HIV) infection, including perinatal transmission, in Africa may have substantial rates of loss to follow-up. A better understanding of the characteristics and the impact of women and children lost to follow-up is needed.

**Methods** We studied predictors and the impact of losses to follow-up of infants born in a large cohort of delivering women in urban Malawi. The cohort was established as part of a trial of vaginal cleansing with chlorhexidine during delivery to prevent mother-to-infant transmission of HIV.

**Results** The HIV infection status could not be determined for 797 (36.9%) of 2156 infants born to HIV-infected mothers; 144 (6.7%) with missing status because of various sample problems and 653 (30.3%) because they never returned to the clinic. Notably, the observed rates of perinatal transmission were significantly lower in infants who returned later for determination of their infection status (odds ratio = 0.94 per month,  $P = 0.03$ ), even though these infants must have had an additional risk of infection from breastfeeding. In multivariate models, infants of lower birthweight ( $P = 0.003$ ) and, marginally, singletons ( $P = 0.09$ ) were less likely to return for follow-up. The parents of infants lost to follow-up tended to be less educated ( $P < 0.001$ ) and more likely to be in farming occupations, although one educated group, teachers and students, were also significantly less likely to return. Of these variables, infant birthweight, twins versus singletons, and maternal education were also associated with significant variation in the observed risk of perinatal transmission among infants of known HIV status.

**Conclusions** Several predictors of loss to follow-up were identified in this large HIV perinatal cohort. Losses to follow-up can impact the observed transmission rate and the risk associations in different studies.

**Keywords** Missing data, HIV-1, perinatal transmission, Africa, vaginal cleansing, simple trials

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Perinatal transmission is a devastating consequence of the spread of the human immunodeficiency virus type 1 (HIV-1) infection epidemic among women of child-bearing age, and is especially common in developing countries where antiretroviral

therapy is not available. Studies of HIV-1 perinatal transmission are needed to estimate its incidence, understand epidemiological associations and test simple, potentially effective interventions in these areas. However, performing large studies in developing

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areas is challenging. One major problem is that many mothers and their infants are lost to follow-up. Some of the same variables that affect loss to follow-up (LFU) rates may also affect mother-to-child HIV-1 transmission risk. An analysis of the profile of women who do not return for follow-up and their infants is needed to understand more about this patient group whose outcomes are unknown.

For a child to be brought back for evaluation in a clinical study, the parent(s) and the child must be alive, remaining in the same geographical area, able to take time from their occupation and to find transportation, and to understand the need for a postnatal visit. Therefore, one may hypothesize that maternal disease factors, predictors of neonatal and infant mortality, residence, education, and occupation may be important predictors of LFU. The objective of this analysis was to determine the predictors of LFU and their potential impact in over- or under-estimation of observed transmission rates and measures of association in an African population. For that purpose we used data from a large HIV-infected cohort enrolled in an intervention trial (vaginal cleansing with chlorhexidine at the time of delivery) that was performed in Malawi.<sup>1</sup>

## Methods

### Description of the Malawi cohort

Details of the methodology and the results of the primary analysis of this study have been published elsewhere.<sup>1</sup> Briefly, the study compared conventional labour and delivery with that using a simple intervention (cleansing the birth canal with a cotton pad soaked in an antiseptic solution of 0.25% chlorhexidine upon admission to labour and every 4 hours thereafter until delivery). During the study period, June to November 1994, 2094 HIV-infected women gave birth to 2156 live children at the Queen Elizabeth Central Hospital in Blantyre, Malawi. All live births from HIV-infected mothers are considered in the analysis. Children without any follow-up visits are considered as LFU. Perinatal transmission risk factors are based on the 1359 children with known HIV status.

Blantyre is the largest urban centre in Malawi. The hospital is a large tertiary care facility offering medical services to the city, but also to some more distant populations. Approximately 14 000 women deliver at the hospital every year. Exact data on residence were not collected, but the setting of the study in an urban hospital was selected such as to ensure that the majority of mothers must have come from the greater urban Blantyre area and thus follow-up should be optimized. In this trial, 2 months of no intervention were followed by 3 months of intervention and a final month of no intervention. The intervention was implemented in alternating periods, because it was anticipated that individual randomization would create record-linkage and misclassification problems, due to the large volume of deliveries. There were no restrictions for eligibility based on education and occupation, although medical personnel were excluded from testing to protect their confidentiality, since many were known to the project staff.

Information about the mother-child pairs was obtained at delivery and at each visit using standardized questionnaires. Mothers' infection status was determined by analyses of cord blood for HIV-1 antibodies. Cord blood specimens were more convenient than using maternal peripheral blood specimens

which would have required an additional venipuncture. Infection status was determined for 1359 (63.1%) of the study infants by polymerase chain reaction (PCR) on dried blood spots collected from heel sticks, done at each visit, at one month of age or older. Based on an analysis of serial samples, we have estimated that a single PCR-positive result is 97% likely to identify an infected infant.<sup>2</sup> In the original analysis of the data (for which only vertex presentation vaginal singleton deliveries qualified), there was no difference (26% versus 27%) in the rates of HIV transmission in the intervention versus the control group.<sup>1</sup>

### Statistical analysis

To investigate infection rates and correlates among children whose parents/guardians are unable to return on time for scheduled follow-up visits, we estimated the HIV prevalence among infants brought back for the first postnatal evaluation at different ages and we compared the profile of social and biological factors of late-coming infants (coming for the first visit after the second month) with the profile of these factors in children lost to follow-up. Then we examined whether we could identify predictors of LFU among variables pertaining to biological (maternal, obstetric, perinatal and infant) and social (educational and occupational) factors. Both single and multiple logistic regression analyses were conducted to identify important predictors.<sup>3</sup> For multiple regressions, a back-elimination procedure used log-likelihood ratio criteria with  $P > 0.1$  for removing variables and  $P < 0.05$  for entering variables. Interactions between the variables selected in the final multivariate model were also considered, but no important ones were identified. We also used a multivariate model to determine significant factors of perinatal transmission among infants with known infection status and evaluated whether predictors of transmission were also predictors of LFU, and vice versa.

We also evaluated the relationship between variables that may be important in LFU. Differences in rates for binary variables according to different categories were assessed by Fisher's exact test and differences for continuous variables in different categories were tested with Mann-Whitney U test for two groups and with Kruskal-Wallis analysis of variance for more than two groups. Correlation between important predictors of LFU was assessed with Spearman's correlation coefficient.

Analyses were performed in SPSS<sup>4</sup> and StatXact.<sup>5</sup> All  $P$ -values are two-tailed.

## Results

By the end of 1997, the HIV infection status had been determined for 1359 (63.1%) of the 2156 infants born to HIV-1 seropositive mothers. Of 797 infants whose status was not determined, 653 (81.9%) were infants who were never brought back for follow-up. With the exception of eight infants who were known to have died in the first 3 months, no survival or HIV status information was available for these 653 infants. In all, 144 (7%) infants were brought back for follow-up but there were problems with the collection, labelling or testing of their samples: 44 provided samples which arrived too late for inclusion in the study; 27 had only a cord blood sample and no further follow-up; and for 73, the sample was not obtained or its identity was uncertain. The only correlate of having a sample problem was being a multiple gestation birth and this occurred

because the identity of the twin giving the sample was sometimes not clearly specified. Otherwise, this heterogeneous group of 144 infants provided no insight into risk factors for lack of follow-up and is excluded from the multivariate analyses of risk of LFU. Their inclusion gave comparable results (not shown).

Of the 1359 infants with known HIV status, 86.8% had their status determined during a visit within the first 2 months of life, while 180 (13.2%) first came for evaluation at 3–24 months of age. As shown in Table 1, there was a decrease in the HIV infection prevalence for infants who were brought back for

determination of their status after the second month. Only 4/43 (9.3%) infants first brought for evaluation after age 8 months tested HIV-positive. Overall, the odds of HIV positivity decreased 0.94 fold for each month of delay for the determination of the infection status ( $P = 0.03$ ). This decrease occurred despite the probability of additional transmission from breastfeeding, since all infants were breastfed. Late-coming children had similar birthweight as lost children (mean 2809 versus 2778,  $P = 0.50$ ) and had marginally better educated mothers (mean 6.24 versus 5.71 years,  $P = 0.10$ ) and fathers (mean 9.34 versus 8.74 years,  $P = 0.03$ ). However, this difference was probably largely due to the fact that 31 lost children had a farmer father, compared with none of the late-coming children. When farmers were excluded, there was no difference between late-coming children and lost children in terms of parental education or occupation. Children who do return for follow-up late are probably not representative of children who never return, but this analysis provides some insight into the characteristics of late-comers and they seem to resemble the profile of lost infants and their parents.

Table 2 shows the association of different biological variables with the rate of LFU. The LFU rates increased when the infant

**Table 1** Documented human immunodeficiency virus (HIV) prevalence rates according to time of determination of HIV infection status

Time HIV status determined	HIV infection rate (Infected infants/total)	Crude relative risk
First month	25.6% (214/836)	1.00
Second month	27.1% (93/343)	1.06
Third month	22.8% (18/79)	0.89
After the third month	18.8% (19/101)	0.73

$P = 0.03$  in a linear logistic regression of infection status on time of determination.

**Table 2** Relation of biological variables with loss to follow-up

Variable	N	Loss to follow-up		Crude relative risk
		n	%	
<b>AIDS signs and/or symptoms</b>				
Yes	286	88	30.8	1.02
No	1870	565	30.2	1.00
<b>Mode of delivery</b>				
Caesarean section	272	76	27.9	0.91
Vaginal	1882	575	30.6	1.00
<b>Gestational age (weeks)</b>				
<38	820	263	32.1	1.12
≥38	1326	381	28.7	1.00
<b>Birthweight (g)<sup>a</sup></b>				
<2000	130	58	44.6	1.54
2000–2500	422	129	30.6	1.07
>2500	1596	459	28.7	1.00
<b>Duration of rupture of membranes (h)</b>				
>4	540	152	28.1	0.92
≤4	1600	486	30.4	1.00
<b>Multiple gestation</b>				
Yes	123	40	32.5	1.07
No	2033	613	30.2	1.00
<b>Severe vaginal bleed on delivery</b>				
Yes	53	11	20.8	0.68
No	2103	642	30.5	1.00
<b>Genital warts</b>				
Yes	58	24	41.4	1.38
No	2096	627	29.9	1.00
<b>Phase of the clinical trial</b>				
Intervention phase	1124	332	29.5	0.95
No intervention phase	1032	321	31.1	1.00

The number of infants across categories of each predictor may not add to 2156 for all predictors due to sparse missing data on predictors. Other variables not showing a significant association with loss to follow-up included Apgar score at 1 and at 5 min, rupture of membranes (yes/no), episiotomy, maternal age, number of pregnancies, fetal presentation, and sex of the infant (not shown in the Table).

<sup>a</sup>  $P = 0.004$  for linear association with loss to follow-up.

**Table 3** Relation of socioeconomic variables with loss to follow-up

Variable	N	Loss to follow-up		Crude relative risk
		n	%	
<b>Maternal education (years)<sup>a</sup></b>				
0-4	683	249	36.5	1.38
5-8	942	264	28.0	1.06
≥9	531	140	26.4	1.00
<b>Paternal education (years)<sup>b</sup></b>				
Less than standard 8 years	358	142	39.7	1.44
Completed standard 8 years	1465	405	27.6	1.00
<b>Maternal occupation<sup>c</sup></b>				
Housewife	1876	572	30.5	1.18
Teacher	34	18	52.9	2.05
Other occupations	229	59	25.8	1.00
<b>Paternal occupation<sup>d</sup></b>				
Farmer	48	31	64.6	2.21
Teacher	37	17	45.9	1.57
Other occupations	1865	545	29.2	1.00

The number of infants across categories of each predictor may not add to 2156 for all predictors due to missing data on predictors. Note in particular that paternal education was unknown for 333 infants, while information on other potential predictors was far more complete.

<sup>a</sup>  $P < 0.001$  for linear association with loss to follow-up.

<sup>b</sup>  $P < 0.001$  for linear association with loss to follow-up.

<sup>c</sup>  $P = 0.4$  for loss to follow-up when all occupations are considered separately (Fisher's exact test).

<sup>d</sup>  $P < 0.001$  for loss to follow-up when all occupations are considered separately (Fisher's exact test).

birthweight was smaller (mean [sd] weight for lost infants 2778 [546] g versus 2848 [497] g in non-lost infants,  $P = 0.004$ ). The proportion of lost infants in the category of <2000 g birthweight was particularly high (44.6%). There was no significant difference between lost infants and non-lost infants in duration of rupture of membranes (mean [sd] 3.78 [5.47] versus 3.91 [5.82] h) and gestational age (mean [sd] 37.6 [2.5] versus 37.9 [2.2] weeks). There was a slightly lower rate of LFU among infants born in the intervention phase as compared with the control phase, but the difference was not significant (odds ratio [OR] = 0.91,  $P = 0.3$ ). There were no statistically significant interactions of treatment arm allocation and other predictors of LFU or missing infection status.

Social factors were important predictors of LFU (Table 3). There was strong evidence that infants born to mothers of lower educational status were more likely to be LFU ( $P < 0.001$ ). The mean years of education (sd) was 5.70 (3.88) in mothers of lost infants compared with 6.44 (3.62) for mothers of non-lost children. A similar association was seen with father's education (mean [sd] in the two groups 8.74 [3.11] versus 9.27 [2.84] years, respectively). Most mothers in the study considered themselves housewives. The only maternal occupation associated with a high rate of LFU was teaching. By contrast, there was significant heterogeneity in the rates of losses for different paternal jobs ( $P < 0.001$  by Fisher's exact test). Among occupations practised by more than 30 fathers in the study, the highest rates of losses were seen for farmers, but losses were also high when fathers were teachers.

Factors related to LFU were also related to each other to a substantial extent. There was a strong correlation between maternal and paternal education ( $r = 0.64$ ,  $P < 0.0001$ ) and, as expected, the type of occupation was related to the number of years of education ( $P < 0.0001$  for both mothers and fathers by

Kruskal-Wallis ANOVA). Higher education correlated modestly with higher birthweight ( $r = 0.13$  for maternal education,  $r = 0.12$  for paternal education), and there was strong evidence that birthweight was also associated with paternal occupation and less so with maternal occupation ( $P < 0.0001$  and  $P = 0.016$ , by Kruskal Wallis ANOVA, respectively).

In a multivariate model shown in Table 4, the important independent predictors for LFU were similar to those suggested by the unadjusted associations. Social parameters were important in the multivariate model with more losses to follow-up of infants born to less educated mothers and fathers. Occupations also retained significant associations, notably the odds of not returning increased fourfold when the father was a farmer, and threefold when the father or the mother was a teacher. Significant increases were also seen when fathers were students or doctor assistants but the numbers were small ( $n = 16$  and  $n = 9$ , respectively). Independent biological predictors of LFU included a lower birthweight, and possibly ( $P = 0.09$ ) the presence of warts in the mother. Twins had better follow-up than singletons in the multivariate model, but the effect had marginal statistical significance ( $P = 0.09$ ).

Several of the predictors of LFU were also predictors of perinatal transmission among infants with known HIV status in the study cohort (Table 4). Thus, transmission rates were higher for infants born to mothers of higher education, and for infants of lower birthweight, while twins had lower transmission rates than singletons. Among the other predictors of perinatal transmission the presence of AIDS signs or symptoms, prolonged rupture of membranes, low Apgar score at 1 min and vaginal (as contrasted to caesarean delivery) were not associated with LFU. Several of the predictors were correlated among themselves, in particular in relation to maternal education. Higher maternal education was associated with higher infant weight at birth

**Table 4** Multivariate models for predicting loss to follow-up for an infant and perinatal human immunodeficiency virus type 1 (HIV-1) transmission

Predictors	Loss to follow-up		Perinatal transmission	
	Odds ratio	P-value	Odds ratio	P-value
<b>Birthweight (per 25% increase)</b>	0.84	0.003	0.79	0.003
<b>Maternal warts</b>	1.62	0.09	NS <sup>a</sup>	NS
<b>Multiple gestation</b>	0.67	0.09	0.44	0.014
<b>AIDS sign or symptoms in mother</b>	NS	NS	1.80	0.007
<b>Apgar 1 (per 1 point increase)</b>	NS	NS	0.86	0.008
<b>Caesarean section</b>	NS	NS	0.56	0.07
<b>Rupture of membranes (per h)</b>	NS	NS	1.02	0.01
<b>Maternal education (per 4 fewer years)</b>	1.21	0.002	0.87	0.05
<b>Paternal education &lt;8 years</b>	1.38	0.015	NS	NS
<b>Paternal occupation</b>			NS	NS
Farmer	4.00	0.0001		
Teacher	2.28	0.017		
Doctor/assistant	3.75	0.06		
Student	2.65	0.06		
<b>Maternal occupation</b>			NS	NS
Teacher	3.02	0.004		

The original models considered initially all the biological variables listed in Table 2 (including those listed in the footnote) and also the socioeconomic variables from Table 3—all occupations practised by at least 40 mothers or fathers and those with more than 50% missing infant infection status data were considered initially. Continuous variables are untransformed, except for birthweight where a logarithmic transformation was used which seemed better fitting to the data. Since there were substantial missing data on paternal education, this parameter was coded as two binary variables: missing data on paternal education (yes, no), and paternal education documented to be <8 years (yes, no)—only the latter was retained in the model. Sensitivity analyses using different imputations for missing data and using paternal education as a continuous variable provided qualitatively similar results (not shown). The presented models were selected with back-elimination of variables (Methods).

<sup>a</sup> Not pertinent/non-significant (the variable was not selected in the respective multivariate model).

( $P = 0.001$ ), and fewer AIDS signs and symptoms being reported by the mother ( $P = 0.003$ ).

## Discussion

Our analysis provides insights from a large HIV-related perinatal intervention study in Africa on the extent and potential implications of missing outcome data which are primarily due to LFU. Despite a parsimonious design that should have maximized retention of mothers and infants, infection status was not determined for more than a third of the infants born during the trial. Most of these infants were never brought back by their parents. Low maternal and paternal education were the strongest independent predictors of LFU. Associations were also seen with farming and teaching/student occupations. Women who were wives of farmers probably left the city to return to their villages. In order to maximize follow-up, previous studies in Malawi were restricted to patients who resided close to the hospital and had lower LFU. Geographical residence restrictions are difficult to implement in a large sample study. The failure of teachers or students (in higher levels of education) might reflect the concern of better educated people about stigmatization from being identified as HIV positive<sup>6,7</sup> or, less likely, their use of private sources of well baby follow-up. Part of the failure to return might have been due to high neonatal and infant mortality rates, which may be substantial even among babies born to HIV-uninfected women. Among infant factors, low birthweight was a risk factor for failure to return, probably because this group had a higher mortality rate than average,<sup>8</sup> although we lack

mortality data on lost infants to support this hypothesis. This may be particularly true of low birthweight pre-term infants rather than infants with intrauterine growth retardation. In this study, LFU rates were highest for infants of very-low birthweight (<2000 g).

These findings are relevant to other studies, in progress or contemplated, to understand and reduce the burden of HIV-1 in developing countries. Missing data pose a challenge to their generalizability. In a West African study,<sup>9</sup> many women did not return for follow-up after an HIV test, which was required for enrolment. Patients who enrolled and completed the protocol may not be representative of the whole population. In the present study, we avoided having an extra step of HIV status determination, by using cord blood to determine HIV status at the time of delivery. This simple approach avoided losses that would affect the generalizability of the study in terms of representing appropriately the general population. We also used routine postnatal care visits as follow-up points in order to avoid requiring extra visits for the purposes of the study. Despite this simple approach, losses were high. Missing data will become an even larger issue with studies that require more complex interventions such as pharmacotherapy with antiretrovirals.

The odds for LFU are higher for mothers and fathers of lower education and for low birthweight children who have a higher risk for early mortality and morbidity. Maternal HIV infection has profound effects on perinatal morbidity and mortality.<sup>10</sup> Clinical studies in developing areas may miss information more commonly among populations that are at the greatest social disadvantage. Studying the efficacy of preventive interventions,

such as simple zidovudine regimens,<sup>11</sup> in these disadvantaged populations is already a challenge. Losses and missing outcome data are not unique to developing countries. They have also been a well-recognized problem in HIV-related trials in developed countries<sup>12-14</sup> and similar predictors, poor health and lower socioeconomic status, are also associated with LFU in these settings as well.<sup>12</sup>

Missing data reflect mothers and their infants who are unlikely to return for even minimal regular medical care unless they receive postnatal care elsewhere, as may be the case for the families of farmers. Continuity of care is important for better clinical outcomes. This may be even more important for interventions that need to be extended beyond the intrapartum period, such as pharmacotherapies.

Our analysis also illustrates the need for cautious interpretation of comparisons of transmission rates among different studies. For example, the transmission risk in children with late first evaluations in this study is a complex mix of increased risk due to late transmission from breastfeeding<sup>15-17</sup> but also reduced risk because high HIV-risk infants may be less likely to survive. The latter effect was more influential than the late transmission effect in this cohort. Some infected infants die early from HIV-associated conditions, but their losses are probably only a minor contributing factor because death from HIV itself is uncommon in the first few months of life.<sup>18</sup> More contributory are infants with conditions such as low birthweight who have high transmission risk<sup>19-21</sup> but who may also die before evaluation, thus distorting the observed transmission risk. If studies have substantially different follow-up times or LFU rates, direct comparisons may not be valid. The current trial was interested more in intrapartum transmission and its prevention. Studies of postnatal transmission are likely to be more severely affected by problems with LFU.

These observations could also impact on the strength of observed associations. As pointed out for birthweight, when the factor under study is associated with both LFU and HIV transmission, the association may weaken when follow-up is done only late, after a substantial number of early deaths have already occurred. In another example, twins have a lower rate of HIV transmission because the second born of twins has a lower infection rate.<sup>22</sup> However, second born twins are also at additional risk of dying at or near birth. This might distort the measurement of HIV status if it is measured late. Other medical conditions which could be associated with both transmission risk and LFU rates include maternal illness from AIDS or other causes, caesarean sections, prolonged rupture of membranes, and markers of prematurity such as low Apgar scores. None of these factors were predictive of LFU in our cohort, but it is possible that some of these factors may become important in cohorts with late infant assessments.

The lower transmission risk in infants of less educated mothers needs to be confirmed, since it was of borderline statistical significance. As with the infant and obstetric factors, the role of lower follow-up rates in the less educated needs to be considered. A possible explanation is that HIV was introduced into higher socioeconomic and urban strata earlier and hence those mothers are on average at more advanced stages of disease with increased transmission risk. However, low educational status may also result in poorer infant care and greater infant mortality, and hence low follow-up rates. Low follow-up rates in parents

of lower socioeconomic status may also result from inability to take time from work or to pay for transportation.

With regard to the intervention trial, which was the source of the data for the current analysis, the losses to follow-up were approximately equal in both groups, and we found no evidence that the losses were unbalanced between arms in relation to predictors of transmission. Thus, there is no reason to suspect the trial results are not reliable. Despite losses, the study was adequately powered to detect modest effects (30% risk reductions). Lost information would still curtail the power of such a study to detect small treatment effects, such as reductions of the transmission risk in the 10% range. Effects of such magnitude may need to be considered in other trials<sup>23</sup> and future meta-analyses,<sup>24</sup> if such small benefits are thought to be clinically meaningful to detect, or if particular subgroups may benefit from the intervention. This may be important, since antiseptic vaginal cleansing has been reported to improve also other outcomes such as perinatal infant and maternal morbidity and mortality.<sup>25</sup>

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