Compliance and loss to follow up of HIV negative and positive mothers recruited from a PMTCT programme in Zimbabwe.

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Abstract

Objective: To describe the methodological challenges of a nine months follow up study of mothers recruited from a national Prevention of Mother To Child Transmission (PMTCT) programme with regards to defaulters, drop outs and compliance.
Design: Nested case control study.
Setting: Three peri-urban clinics in Zimbabwe namely: Epworth, St Mary's, Seke North.
Method: Pregnant women who enrolled at 36 weeks of gestation were recruited for a follow up of mother and child from delivery, six weeks, four and nine months *post partum*. Follow up trend of these women was compared between the HIV positive and negative mothers with regards to defaulting, drop outs, full and partial compliance. Statistical significance was computed using the Chi-square test.
Results: Of the enrolled 1 050 pregnant women with a known HIV status (594 HIV negative and 456 HIV positive) 851 (457 HIV negative and 394 HIV positive) showed up at one or more visits scheduled up to nine months. The denominator was dropping at each point and time. The overall dropout rate was 19% without a significant difference between the HIV positive and negative women at delivery. At six weeks the drop out rate was 35 (7.7%) for the HIV positive versus 75 (12.9%) p=0.010 and at four months 12 (2.9%) versus 39 (7.7%) p=0.002 respectively. However, at nine months the drop out rate was not different (p=0.747). The defaulter rate was significantly different at every stage between the HIV positive and negative mothers from delivery to six weeks, becoming even more significant at the four and nine months visit (p=<0.001). The overall full compliance at nine months was 46.1% with a significant difference between the HIV positive (55.6%) versus (37.9%) for the HIV negative (p=<0.001).
Conclusion: Drop out is highest among the HIV negative as opposed to the HIV positive with the peak period being at "six weeks". There is high defaulting among the HIV negative compared to the HIV positive with the peak being at "four months". The study has shown that the HIV negative women are more likely to drop out whereas the HIV positive were twice as likely to fully comply. It is surprising that the peak drop out period, "six weeks visit" is a cardinal existing national scheduled visit where both mother and baby undergo a full medical examination with the mother having a pap smear taken.

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Introduction

In any clinical trial, loss to follow up presents a complexity regarding the validity of the final sample. Follow up data in HIV research programmes are often incomplete due to high attrition caused by defaulting, refusal to continue, death and some other reasons.[1] A better understanding of the methodology of a study and the dynamics of losses to follow up is needed to devise interventions that can minimize their effects.

PMTCT is a programme that offers an avenue for various studies of pregnant women both HIV positive and negative together with their index babies. However, recruiting clients from an existing programme with its own objectives has advantages and disadvantages.

The challenges are in terms of burdening an already overwhelmed infrastructure; personnel handling the clients; information given to the same participants; rules and regulations of the study and the waiting time whilst going through the procedures of the study. Follow up of mother and infant pairs can be problematic for various reasons mainly cultural norms pertaining to handling of neonates, social and demographic characteristics of the mothers and service provision based on the recruitment and counselling component.[2] Problems of attrition have been reported not only in HIV/AIDS research but in other fields of health and their impact on follow up studies continue to pose challenges on both design and power of the study to generalize results.[3,4]

Highlighting such challenges will help prospective researchers in identifying some of the issues that need to be addressed and adjusted for when estimating sample size so as to have adequate power at the analysis stage. The main focus is on trying to highlight ***when, how*** and ***where***, possible ***why*** participants are retained and lost in the follow up. These issues will be linked to the most commonly used terms: ***drop out, defaulter and compliance*** and their appropriateness in describing the events in the follow up of mothers and their babies within a desired study time frame. The main purpose of this paper is to describe the process of designing, recruiting and following up pregnant women enrolled from a PMTCT national programme, highlighting the methodological challenges encountered in modern research in an environment driven by operational research. It would also help to assess the follow up trend from enrolment, delivery, six weeks, four months and the nine months visit.

Background

Description of the PMTCT National Programme: Zimbabwe continues to have one of the highest HIV infection rates in the world, observed to be 31.1% among women of fertile age in 1999.[5] In 2002 the HIV prevalence among antenatal clinic (ANC) attendees was estimated to be 25.7%.[6] The government of Zimbabwe embarked on a Prevention of Mother to Child Transmission (PMTCT) of HIV initiative with a pilot project in 1999 and adoption of a national programme in 2002.

All women attending ANC are offered voluntary counselling and testing (VCT) for HIV and those that are found positive given Nevirapine at 36 weeks of gestation to self administer at the onset of labour. Their babies are given NVP within 72 hours of delivery.

It is within this national programme that our study, the STI/HIV and Child Development Project was designed and whereby subjects were recruited. The objectives of the study were:

To assess the role of sexually transmitted infections (STIs) on Mother to Child Transmission (MTCT) of HIV and the impact of a single dose of Nevirapine (NVP) given to babies born to HIV positive mothers on their neurological development compared to children born to HIV negative mothers. To describe and compare the growth pattern and neurological development of children exposed to **omega-3** *tablets and those not exposed.*

To describe the incidence of STIs and HIV among women enrolled into PMTCT.

Materials and Methods

The study was conducted in three maternal child health clinics in peri-urban areas around the capital city of Harare, (namely Epworth, Seke North and St Mary's) in Zimbabwe. Women were enrolled into the study from 36 weeks of gestation after being pre- and post test counselled for HIV infection as part of the National programme on PMTCT. Recruitment was done in phases. The first phase being from March to September 2002 where all pregnant women regardless of HIV status were consecutively enrolled. However, as it proved difficult to get the desired number of HIV positive women, from January 2003 it was mainly HIV positive women that were recruited. Within this cohort 108 women (42 HIV negative and 66 HIV positive) were recruited to form an **omega-3** sub study. These women received **omega-3** tablets from 36 weeks of gestation to six months post delivery.

Women were followed up, from delivery, six weeks, four months, nine months post delivery. Clinical and laboratory parameters were observed and analyzed from both mothers and their babies.

Design of the study: A nested case control study.

Study sites included: Three peri-urban clinics around Harare, offering maternal and child health services (Epworth, St Marys and Seke North clinics).

Study population: Pregnant women at 36 weeks of gestation booked at the respective study sites (ANC) having gone through VCT under the national PMTCT programme.

Sample size: It was calculated at 900 pregnant women, 600 seronegative and 300 sero positive allowing for 20% loss to follow up and ensuring enough sample size power for analysis.

Client eligibility: Included women in the national VCT/PMTCT programme, who were 36 weeks pregnant and at least 18 years old. They had all been post test counselled for HIV, given their HIV results and

signed an informed consent sheet.

Clients were excluded if they were currently enrolled into another ongoing study, had proven sickle cell disease or bleeding disorders, were allergic to benzodiazepines, and were on current anti TB treatment and reported an abnormal blood chemistry.

Baseline Investigations: Women responded to a questionnaire sourcing socio- demographic history and knowledge of STI/HIV signs and symptoms as well as feeding practices post natally. All underwent a physical examination, including a gynaecological speculum examination and abdominal palpation. Blood samples and a high vaginal swab were collected.

Follow up: After enrolment the first follow up was at delivery. During this stage the mode of delivery was noted together with anthropological measurements of the neonate, and for the HIV positive time between taking of NVP and delivery was documented.

Cord blood was collected from the baby for HIV- PCR analysis. There were three follow up time points after delivery, being at six weeks, four months and nine months whereby both mother and baby had a physical examination, blood samples collected and for the mothers a high vaginal swab (HVS) together with a pap smear. Infant feeding practices were also assessed.

A neurological and developmental test using a standardized tool, the Bayley Infant Neurodevelopmental Screener **(BINS)** was performed between three to nine months after delivery.

Definition of terms used.

Drop out (DO): A person enrolled in a study who becomes inaccessible or ineligible for follow up, due to either inability including dying or unwillingness to remain enrolled.

In summary DO = those that could not be accessed plus those refusing to continue with the study + those who died during the follow up period.

Defaulter: One who is initially enrolled and appears at one visit but does not turn up for the subsequent scheduled visit for some reason and then reappears at some point during the follow up. They are defined as first or second time defaulters and when they default completely (complete defaulter) they become a drop out at the end point.

Compliance: Comprises those subjects enrolled into a study who report for each of the designated visits. Compliance is divided into two.

1) *Full:* referring to those reporting for all the stipulated visits throughout the study.

2) *Partial*: those appearing at one visit and defaulting on one or more visits.

Ethical Clearance.

The study was approved by both the Ethical Review Committee in Norway and the Medical Research Council of Zimbabwe.

Statistical Analysis.

Data was analysed using the Statistical Package for the Social Sciences version 11.0 (SPSS, Chicago, IL). Chi-square test was used to assess the differences in attendance proportions between the HIV negative and HIV positive mothers. Level of significance was observed for a p value less than <0.05 and 95% confidence interval (CI).

Results

Enrolment: A total of 1 050 pregnant women with known HIV status (594 HIV negative and 356 HIV positive) consented to participate in our study. Of these only 851 (81%) reported for one or more visits of the scheduled nine months follow up.

***Description of the enrolled women*:** The women had a mean age of 23.7(SD 5) for the HIV negative and 25.9 (SD 4.9) for the HIV positive ($p<0.001$).

They reported a mean (SD) pregnancy rate of 2.03 (1.1) and mean live births of 0.9 (1.1) for the HIV negative versus 2.5 (1.2) and 1.6 (1.2) for the HIV positive respectively ($p<0.001$. Table I shows the comparison of socio-demographic characteristics of the mothers according to HIV status.

Table I: Sociodemographic characteristics of the women.

	Total	HIV NEGATIVE	HIV POSITIVE	p value
Marital status				
Single	77	33 (42.9%)	44 (57.1%)	
Married	967	560 (57.9%)	407 (42.1%)	0.010
Income				
Generates Income	256	119 (46.5%)	137 (53.5%)	
No income generation	794	475 (59.8%)	319 (40.2%)	>0.001

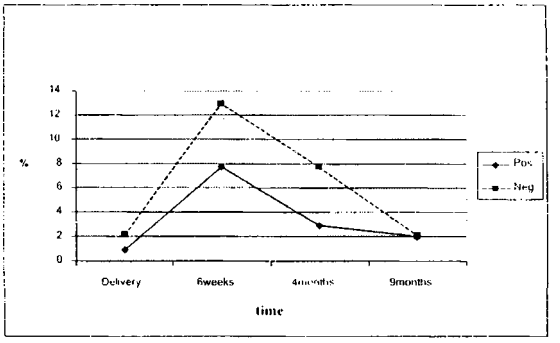
Drop outs: Overall, a total of 199 (19%) mothers of the 1 050 dropped out over the nine months follow up. The drop out was highest at the six weeks visit, with a significant difference between the HIV positive and negative women at four months. At nine months it was no longer different (Table II).

Table II: Comparison of drop out rate by HIV status from delivery, six weeks, four months and nine months.

Time frame	Total	HIV Negative	HIV Positive	p value
	N=1050 (%)	N=594 (%)	N=456 (%)	
Delivery	17 (1.6)	13(2.2)	4(0.9)	0.155
		N=581	N=452	
6 weeks	110(10.6)	75(12.9)	35(7.7)	0.010
		N=506	N=417	
4 months	54(12.1)	39(7.7)	12(2.9)	0.002
		N=467	N=405	
9 months	21(2.4)	10(2.1	11(2.7)	0.741
Overall drop out	**199(19)**	**137(23.1)**	**62(13.5)**	**0.001**

The drop out trend increased from delivery, reached a peak at six weeks and steeply declined at four months in both the HIV positive and negative mothers (Figure 1).

Figure I: Drop out rate comparing the HIV negatives and HIV positives.



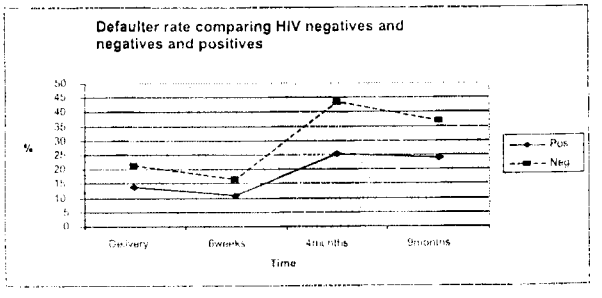
Defaulters: Overall there is high defaulting which is significantly different between the HIV positive and negative women from delivery to nine months. At four months it reaches a peak with the highest defaulters who are notably higher among the HIV negatives 220 (43.5%) versus 106 (25.4%) for the HIV positives (Table III).

Table III: Comparison of the defaulter rate between HIV positives and negatives.

Time	Total	HIV -ve	HIV +ve	p value
	N=1050 (%)	N=594 (%)	N=456 (%)	
Delivery	190 (18.1)	127 (21.4)	63 (13.8)	0.002
		N=581	N=452	
6 weeks	145 (14)	96 (16.5)	49 (10.8)	0.012
		N=506	N=417	
4 months	326 (35.8)	220 (43.5)	106 (25.4)	<0.001
		N=467	N=405	
9 months	270 (31)	173 (37)	97 (24)	<0.001

Trends in the defaulter rate show a slight decline from delivery to six weeks and a steep increase at four months which is more pronounced among the HIV negatives, declining again at nine months. For the HIV positives after four months it stabilized (Figure II).

Figure II: Comparison of time point compliance by HIV status.



Compliance: Overall the HIV positive mothers complied more partially and fully compared to the HIV negatives. There is a significant difference in the time point compliance between the HIV negative and positive mothers from delivery up to nine months p=<0.001. The difference is more pronounced at the four months visit where it drops below 50% among the HIV negatives, being more than 20% compared to the HIV positives at that point. (Table IV).

Table IV: Comparison table of time point compliance by HIV status.

Time frame	Total mothers complying	HIV Negative	HIV positive	p value
Delivery	N=1050 (%) 843 (80.3)	N=594 (%) 454 (76.4)	N=456 (%) 389 (85.3)	<0.001
6 weeks	778 (70.6)	N=581 410 (70.6)	N=452 368 (81.4)	<0.001
4 months	546 (59.9)	N=506 247 (48.8)	N=417 299 (71.7)	<0.001
9 months	581 (66.6)	N=467 284 (60.8)	N=405 297 (73.3)	<0.001

Compliance is consistent from delivery up to the six weeks visit and drops at four months, stabilizing at the nine months visit. The gap is more pronounced at the four months visit where there is a sharp drop among the HIV negatives dropping below 50% and picking up slightly at the nine months visit (Figure III).

Figure III: Trends in compliance of mothers by HIV status.

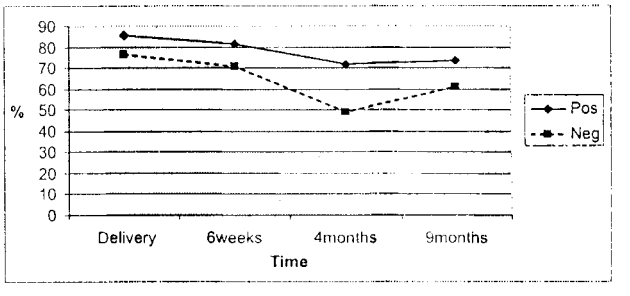


Table V: Association between HIV status and compliance.

Compliance status	HIV STATUS		Total	p value
	Negative	Positive		
Full compliance	173 (37.9)	219 (55.6%)	392 (46.1%)	<0.001
Partial Compliance	284 (62.1%)	175 (44.4%)	459 (53.9%)	
	457 (100%)	394 (100%)	851 (100%)	

Discussion

The study has demonstrated that there is a high drop out rate which is more pronounced among the HIV negatives than the HIV positives. Of note is the fact that HIV positives are twice more likely to fully comply. This is because of HIV and opportunistic infections, as these mothers might need continued care whereas the HIV negative mothers do not see the immediate benefit of being followed up or visiting a clinic.

The drop out threshold is at the six weeks visit in both HIV positive and negative mothers; various explanations can be attributed to this. The main reason is the traditional belief of not taking the neonate outside the house until a certain specified time. Ironically the six weeks post delivery visit is the existing scheduled routine national *post natal* visit whereby both mother and baby have a full medical examination and the mother has a pap smear taken. One would anticipate an overwhelming turn up at this particular visit.

However, utilizing such cardinal study follow up time points in air follow up did not seem to be of any benefit. This is in agreement with other studies, including those involving HIV/AIDS and those outside this field.[2,3]

The decrease in drop outs at nine months for both groups is most likely due to the continued information about the study, more attention from the study personnel and the availability of free medication. On the other hand living in a high HIV prevalent country some of the HIV negatives at enrolment could have sero converted, thereby presenting with medical problems and realizing the benefits of returning to the study.

The high attrition rate is comparable to other HIV studies that reported a follow up loss of 20 to 30% and compliance of 52% to 65%.[1,2,8] In a study from Malawi it is even highlighted that follow up studies after birth are likely to be affected by high drop outs.[2]

There is generally high defaulting which is more pronounced among the HIV negatives compared to the HIV positive women.

The highest drop out is at the four months visit. This is most likely because at this period the mothers are no longer accessing any ANC service and thus take their babies to the "under five clinic" for immunizations. It becomes difficult to locate them as they report for the immunizations in other departments. In addition it may also not be the biological mothers bringing along the baby, thereby the mother will miss out on the study visit. As for the HIV negative, as long as they are healthy, they might not feel obliged to report to the study.

The overall compliance demonstrates that those who are convinced to stay in the study initially are the ones who are usually successfully followed up. More HIV positive women comply fully whilst the HIV negatives comply more partially. This is mostly due to the perceived immediate benefits which are more apparent and tangible for the HIV positives as opposed to the HIV negatives who enter in and out of the study as they wish. The HIV positive are eager to know more about their own health status and that of their babies. Where as the HIV negative respond according to their needs at that particular point and time.

It is necessary to put extra effort into retaining participants once they miss one follow up visit in the initial phase. The challenge is defining the threshold period, in order to keep as many people in the cohort and ensuring that they comply fully.

Limitations: The major limitation lies in the design of the study where recruitment was done in phases with at least four months difference between the first group and the following one. Using different study sites could also have a negative impact on the follow up process as was pointed out previously.[8]

The women could also be overwhelmed with regards to counselling and information especially since they were recruited from another programme with its own objectives.

Conclusion

There is high attrition of participants due to increased defaulting and drop outs among the HIV negatives compared to the HIV positives. The threshold for dropping out is at six weeks post delivery whilst it is four months for defaulting. Full compliance is observed more frequently for the HIV positive.

Maximum effort should be put into retaining participants in the initial follow up. For that, future studies should find out the predictors and behavioural characteristics of those that drop out, the defaulters, and those who remain in the study.

The counselling component should emphasize the importance of follow up even to the seronegative who regard themselves as not at risk.

In the era with antiretroviral (ARVs) provision, monitoring of the treatment and continuous evaluation of the programme and survival of those affected and exposed is pivotal to a successful implementation.

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