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Responses to Reviewers comments

Please find attached our final revised version. The only request in the last communication was that the manuscript should be shortened.

The abstract is still 250 words and the article itself now has 3504 words.

Thank you for the opportunity to publish in the journal.

Kind regards

Nigel Rollins

1 **Abstract**

2 **Objectives.** To determine the late HIV transmission and survival risks associated with
3 early infant feeding practices.

4 **Design.** A non-randomised interventional cohort.

5 **Methods.** HIV-infected pregnant women were supported in their infant feeding choices.
6 Infant feeding data were obtained weekly; blood samples from infants were taken
7 monthly to diagnose HIV infection. 18-month mortality and HIV transmission risk were
8 assessed according to infant feeding practices at 6 months.

9 **Results.** 1,193 live-born infants were included. Overall 18-month probability of death
10 (95%CI) was 0.04 (0.03-0.06) and 0.53 (0.46-0.60) for HIV-uninfected and infected
11 children, respectively. 18-month probability of survival was not statistically significantly
12 different for HIV-uninfected infants breastfed or replacement fed from birth. In univariate
13 analysis of infant feeding practices, the probability of HIV-free survival beyond the first 6
14 months of life in children alive at 6 months was 0.98 (0.89-1.00) amongst infants
15 replacement fed from birth, 0.96 (0.90-0.98; $p=0.25$) and 0.91 (0.87-0.94; $p=0.03$) in
16 those breastfed for less or more than 6 months, respectively. In multivariable analyses
17 maternal unemployment and low antenatal CD4 counts were independently associated
18 with more than three-fold increased risk of infant HIV infection or death.

19 **Conclusions.** Breastfeeding and replacement feeding of HIV uninfected infants were
20 associated with similar mortality rates at 18 months. However, these findings were
21 amongst mothers and infants who received excellent support to first make, and then
22 practise, appropriate infant feeding choices. For programmes to achieve similar results,
23 the quality of counselling and identification of mothers with low CD4 counts need to be
24 the targets of improvement strategies.

**Infant feeding, HIV transmission and mortality at 18 months:
The need for appropriate choices by mothers and prioritisation within programs**

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4

5

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25

26

27

- 1 **Running title:** Early infant feeding and 18m HIV-free survival
- 2 **Key words:** Mortality, HIV infection, transmission, infant feeding, maternal health
- 3 **Word count:** 3504
- 4 **Abstract:** 250
- 5
- 6

1 **Introduction**

2 The dilemma of how best to feed infants and young children of HIV-infected mothers
3 living in high HIV prevalent communities remains complex. Exclusive breastfeeding
4 carries a lower risk of HIV transmission over the first 6 months of life(1) but is infrequently
5 practised by mothers or effectively supported by health systems(2;3). Replacement
6 feeding avoids all postnatal HIV transmission but carries the risk of death(4;5) when
7 given in household circumstances that are not ideal. Early data suggest that highly active
8 antiretroviral treatment (HAART) given to HIV-infected mothers during the period of
9 breastfeeding can reduce transmission risks, even if she is already immunodeficient (6-
10 9). Yet despite 15 years of effective therapeutic interventions being available to reduce
11 peripartum transmission of HIV, more than 500,000 children become infected by this
12 route each year highlighting the gap between scientific evidence and feasibility or
13 coverage of prevention of mother-to-child transmission of HIV (PMTCT) programmes.
14
15 Although not commonly measured in programmes, child survival without HIV infection,
16 rather than avoidance of HIV infection alone, has emerged as the most important
17 measure of PMTCT effectiveness(10). This acknowledges not only the availability and
18 effectiveness of therapeutic interventions but also the competing threats to child survival.
19 The quality of counselling to guide women in their choice of infant feeding practice and
20 the practical support to enable these choices is frequently deficient(11;12). As a result,
21 sub-optimal feeding practices have resulted in high mortality of HIV-exposed infants(13).
22
23 While the transmission risks of infant feeding practices of HIV-infected mothers in the first
24 6 months of life has been substantially researched, the pattern of feeding beyond this
25 period is equally important in determining child survival. This paper describes the
26 outcomes of infants that were part of an intervention cohort study in which feeding
27 practices were intensively supported. We report the 18 month HIV-free survival of HIV-
28 exposed infants according to infant feeding practices implemented at birth and secondly,

by infant feeding practices between 0-6 months and subsequent feeding practices beyond 6 months of age.

Methods

The study design and methods have been described previously(1). In brief, HIV-infected pregnant women attending rural and semi-urban antenatal clinics in KwaZulu Natal (KZN) were enrolled into a non-randomised intervention cohort study. All women were counselled antenatally regarding infant feeding options and supported in their choice(14); those who chose to formula feed their infants were visited at home antenatally and shown how to safely prepare feeds(14). Mothers were visited at home by infant feeding counsellors three or four times in the first two weeks of life and every two weeks thereafter until the infant was 6 months of age(1). Mothers who chose to replacement feed and who encountered problems were principally supported by the infant feeding supervisor or study nurses when referred by infant feeding counsellors following a home visit or when they visited the study clinics. Mothers and infants were followed-up at the study clinic when the infant was 6 weeks old, every month thereafter until the infant was 9 months of age and then three monthly until 18 months of age. At each visit a dried blood spot sample was collected for determination of HIV status by quantitative HIV RNA assay (Nuclisens HIV-1 QT, Organon Teknika, Boxtel, The Netherlands and Nuclisens EasyQ HIV-1, Biomerieux, Boxtel, The Netherlands)(15;16). HIV status was determined at 5 months to guide counselling on infant feeding practices after 6 months. An independent group of field monitors visited mothers at home every week from birth until the infant was 9 months of age and documented all feeds and morbidity episodes for each day of the preceding week.

1 When infants were 5 months old, breastfeeding mothers were counselled to stop
 2 breastfeeding (at 6 months) of infants that were confirmed HIV uninfected; mothers were
 3 counselled to continue breastfeeding infants who were already HIV infected(17). All
 4 mothers were counselled regarding the introduction of complementary feeds. Single-
 5 dose nevirapine was provided to all HIV-infected women and their infants for use during
 6 labour and delivery and cotrimoxazole was provided to all HIV exposed infants. Six
 7 months supply of commercial infant formula was offered free through the KZN PMTCT
 8 programme from the end of 2002(1;18). CD4 counts were performed on HIV-infected
 9 women antenatally but were not routinely considered in infant feeding counseling. At
 10 each clinic visit, all mothers were checked for symptoms and weight, and referred to the
 11 local hospital for diagnostic services if indicated. At the time of the study, HAART was not
 12 available through the Provincial health services. The study was approved by the
 13 Biomedical Research Ethics Committee of the University of KwaZulu-Natal (T050/01).

14

15 Statistical methods

16 Analysis was based on a database created in April 2007, and included live-born children
 17 of HIV-infected mothers. Cumulative HIV-free survival probabilities in the first 18 months
 18 of life were assessed by Kaplan-Meier analysis(19); associations with maternal and
 19 infant variables were quantified in Cox regression analysis(20). The following variables
 20 were tested in univariable analysis to assess the determinants of HIV infection and
 21 death: multiple birth outcome, sex of the child, maternal education, water access, low
 22 birth weight (<2.5kg), maternal employment, maternal antenatal CD4 count. Variables
 23 with a p-value <0.20 were included in multivariable analysis(20).

24

25 Feeding categories were determined from the analytical database by applying algorithms
 26 that first classified infants' feeding practices on each day of life and then determined the
 27 cumulative pattern from birth. World Health Organization definitions for exclusive

breastfeeding, mixed breastfeeding and replacement feeding were used to classify children from the time of introduction of these fluids or feeds(21-23). A child who was only ever breastfed by his/her mother while having never received any other drink, food or non-human milk with the exception of drops or syrups consisting of vitamins, mineral supplements or medicines was defined as exclusively breastfed. A child who was breastfed at a given age while also having received water-based drinks, food-based fluid, solid food or non-human milk was mixed breastfed from the date of introduction of these fluids or foods. Replacement feeding was defined as giving any non-human milk and the exclusion of all breastmilk, with or without other liquids or solids.

18-month HIV-free survival was assessed according to firstly, infant feeding practices implemented at birth, and secondly, on cumulative feeding recall histories. If exclusively breastfed infants were given additional fluid or milk even on one occasion, they were immediately reclassified as mixed feeding, irrespective of subsequent feeding practices. Infants with no feeding or test data were excluded from the analyses. In case of missing data, information was censored at the time the infant was last seen. To assess HIV-free survival in children breastfed for less and more than 6 months, we had to take into account survival bias, since children needed to be alive at 6 months of age to be breastfed beyond that age. We thus calculated the probability of HIV-free survival between 7 and 18 months of age, according to infant feeding practices from birth until 6 months of age, among children who were still alive, HIV uninfected at 6 weeks and still being followed-up in the cohort at 6 months of age.

All statistical analyses were carried out using SAS software (version 9.1; SAS Institute, <http://www.sas.com>).

Role of the funding source

Wellcome Trust and Sidaction did not contribute to, or influence the study design, implementation, analysis or drafting of the manuscript.

Results

Overall 18-month HIV-free survival

Details of the cohort are shown in Table 1. 1193 live-born infants from HIV-infected mothers born between end-October 2001 and mid-April 2005 were included. By 18 months of age, 147 children died and 237 were diagnosed as HIV-infected; 113 deaths (77%) occurred among HIV-infected children. The overall estimated 18-month probability of death (95% confidence interval) was 0.04 (0.03-0.06) for HIV-uninfected and 0.53 (0.46-0.60) for infected children. Infected children were 17-times more likely to die than uninfected children (unadjusted hazard ratio: 16.9 [11.5-24.8]). By 18 months an estimated 21% (19%-23%) of children born to HIV-infected mothers would have acquired HIV infection. Combined, the overall probability of remaining free from HIV infection and death by 18-month was 0.76 (0.73-0.78). The overall estimated risk exposure for breastfeeding over the 18 month period was 9.1 cases per 100 child-years of breastfeeding (95%CI: 5.8-12.5).

In univariate analyses low birth weight (<2.5kg), maternal unemployment and low maternal antenatal CD4 count were associated ($p<0.20$) with increased child death or HIV-infection and were therefore included in a multivariable analysis. Overall adjusted hazard ratios (AHR) of HIV infection/death were 1.5 (1.1-2.2, $p=0.03$) for low birth-weight children, 1.9 (1.3-2.9, $p=0.004$) for children of unemployed mothers and 2.4 (1.7-3.2, $p<0.001$) for children of mothers with an antenatal CD4 count below 200 cells/ml.

1 **18-month HIV-free survival according to infant feeding practices implemented at**
2 **birth**

3 Among the 1,193 infants, infant feeding practices implemented at birth were: 937 (78%)
4 exclusively breastfed, 105 (8.8%) mixed fed of whom 75 (71.4%) received breastmilk
5 plus water based drinks or solids and 30 (2.6%) breastmilk plus formula milk, and 118
6 (10%) had received replacement milk only. 33 infants were excluded as they had
7 received only water or were fed intravenously from birth (13) or were missing infant
8 feeding data (20).

9
10 Table 2 shows the probability of remaining free from HIV infection and death, as well as
11 the probability of survival according to infant feeding practices implemented at birth. By
12 18 months of age an estimated 25% of infants ever exclusively breastfed born to HIV
13 infected mothers would have acquired HIV infection or have died, compared to 20% of
14 never breastfed infants ($p=0.05$). This difference is mostly due to acquisition of infection
15 through breastfeeding. The 18-month probability of survival among HIV-uninfected
16 children was 96% (94%-97%) regardless whether they were breastfed or replacement
17 fed from birth.

18

19

1 **HIV-free survival according to infant feeding practices from birth until age 6-** 2 **months**

3 Of the 893 children included (not HIV-infected peripartum and still alive at 6 months -
 4 Table 1), 69 (8%) were never breastfed, 136 (15%) were breastfed for less than 6
 5 months, and 688 (76%) breastfed beyond 6 months of age. Cumulative feeding practices
 6 at three and six months of age are shown in Table 3.

7
 8 Of the 688 children who received breastmilk beyond 6 months of age, 278 (31%) had
 9 been exclusively breastfed throughout the first 6 months of life, 42 (5%) received liquids
 10 other than non-human milks at least once and 368 (40%) received food-based fluid, solid
 11 food or non-human milk in the first 6 months of life. Amongst these 688 children the
 12 overall median duration of breastfeeding was 283 days (inter-quartile range: 206-491)
 13 and the Kaplan-Meier probabilities (95%CI) of still being breastfed at 7, 9, 12 and 18
 14 months of age were 0.74 (0.71-0.78), 0.58 (0.54-0.61), 0.45 (0.41-0.49), 0.22 (0.19-0.25),
 15 respectively.

16
 17 Univariable and adjusted analyses of the risk of HIV infection or death between 7 and 18
 18 months in 893 infants alive at 6 months showed a 2.7 increased risk for infants who
 19 continued to be breastfed beyond 6 months compared to the group who were either
 20 replacement fed, exclusively breastfed up to 6 months or ceased all breastfeeding any
 21 time before 6 months (Table 4). In a similar analysis but stratified on antenatal maternal
 22 CD4 count: the adjusted hazard ratio for infants breastfed beyond 6 months was 4.3 (0.9-
 23 18.0; p=0.06) among women with CD4 count below 200 cells/ml and 2.5 (1.0-6.2;
 24 p=0.05) among women with CD4 over 200 cells/ml. Mothers who breastfed for less than
 25 6 months (n=136) were more often unemployed than the mothers who continued to
 26 breastfeed beyond 6 months (n=688) (19.9% vs. 11.5%, p=0.001); they also tended to
 27 more often have access to piped water inside their home (9.5% vs. 7.7%, p=0.25).

1 Mothers in both groups had similar levels of education and access to toilets. The mean
 2 antenatal CD4 count was slightly lower in mothers who breastfed less than 6 months
 3 (487 vs. 514, $p=0.24$) and the proportion of women with CD4 counts below 200 was also
 4 similar (BF<6 months 10.8% vs. BF>6 months 8.1%, $p=0.31$). In multivariable analyses
 5 maternal employment was associated with a three-fold increased likelihood of HIV-free
 6 survival between 7 and 18 months in children alive at 6 months (Table 4); antenatal
 7 maternal CD4 count below 200 cells/ml was associated with a 3.6-fold increased risk of
 8 HIV infection or death. Although low birthweight was associated with survival early in life,
 9 this was not the case for HIV-free survival between 7 and 18 months of age ($p=0.52$).

10

11 The probabilities of death and postnatal HIV acquisition between 7 and 18 months of age
 12 are shown separately in Figure 1. Univariably, the probability of HIV-free survival (no
 13 corresponding figure) at 18 months (conditional on survival to 6 months and including
 14 postnatal transmissions) was 0.98 (0.89-1.00) in the 69 replacement fed from birth
 15 infants, 0.96 (0.90-0.98) in 136 children that were breastfed for any period up to 6
 16 months ($p=0.25$), and 0.91 (0.87-0.94) in 688 children who were breastfed for more than
 17 6 months ($p=0.03$). Overall, the probability of HIV-free survival was significantly lower in
 18 children who were breastfed for more than 6 months than in the combined group of
 19 children replacement fed or breastfed for less than 6 months (0.91 (0.88-0.93) vs. 0.96
 20 (0.93-0.98), $p=0.001$).

21

22 Overall, breastfeeding beyond 6 months increased the risk of HIV acquisition (AHR 3.3;
 23 CI: 1.0-10.5, $p=0.05$) compared with durations of breastfeeding less than 6 months.
 24 However, in multivariable analysis allowing for infant's HIV infection (data not shown),
 25 with replacement feeding only from birth as reference, the probability of survival beyond
 26 6 months of age (excluding deaths in the first 6 months) did not differ by breastfeeding

duration: infants breastfed for less than 6 months AHR 1.2 (0.1-11.9, $p=0.86$); breastfed for more than 6 months AHR 0.9 (0.1-7.1, $p=0.92$).

Among the infants breastfed beyond 6 months of age, although the differences in overall probability of death or HIV infection between 7-18 months in these three groups did not reach statistical significance, those who were exclusively breastfed in the first 6 months tended to do better than those mixed-fed.

Discussion

The most striking, though not new, message from these data is that HIV infection is the major driver of childhood mortality in these rural and urban communities. About 53% of infants who became infected would have died by 18 months compared with 4% of infants who were not. This again emphasizes the gains for child survival if effective PMTCT programming were achieved(24;25).

In this population, replacement feeding of HIV-uninfected infants between 7 and 18 months, or those who were switched earlier, did not increase mortality compared to infants who continued to receive breastmilk. It is essential however, to contextualize these findings including the circumstances that guided the initial feeding choices of these mothers(14) and the support available to them, before simple generalizations are drawn. Mothers who had limited access to safe water, poor sanitation at home, as well as higher CD4 counts tended to initiate breastfeeding; mothers with lower CD4 counts and access to personal income tended to start replacement feeds(14). Mothers also received ongoing guidance and support in their feeding choice and had immediate access to study teams at clinics. The sum of these 'interventions' are likely to have optimized the environment in which these feeding choices were practised and reduced potential

1 morbidity and mortality. This is evidenced by results of an operational study describing
2 the South African national PMTCT programme(3) in which infants of women who were
3 given replacement feeds under inappropriate conditions experienced the highest risk of
4 HIV transmission or death (AHR 3.63; 95%CI 1.48-8.89) in comparison to those who
5 received replacement feeds under appropriate circumstances.

6
7 We were unable to determine if there had been changes in household circumstances
8 from the antenatal period that might have influenced mothers' decisions to switch from
9 breastfeeding to non-breastfeeding in the postpartum period. Antenatal demographic and
10 socio-economic characteristics were available, but although counsellors and nurses
11 would have learned of changes in mothers' circumstances and this would have
12 influenced subsequent counselling, this information was not systematically captured in
13 the database. All HIV-infected mothers had been counselled, both antenatally and
14 postpartum, to stop breastfeeding around 6 months, as long as there was a safe and
15 nutritionally adequate alternative. In spite of this, 688 (77%) mothers of infants uninfected
16 at 6 months decided to continue breastfeeding. Amongst this group 22% would have
17 continued to at least 18 months. For these infants, although at continued risk of HIV
18 infection, this strategy might still have been correct to promote their long term overall
19 survival. Given that this was not a randomized trial, we are unable to determine what
20 might have happened if those same mothers had chosen to stop breastfeeding earlier
21 and adopt a feeding practice that could not have been safely supported.

22
23 Continued breastfeeding resulted in significantly more infections over the 18 month
24 period. Children who were breastfed for more than 6 months were 2.7 times more likely
25 to become infected compared to infants who were breastfed for less than 6 months. The
26 low risk of death, apart from HIV transmission, highlights the feasibility of supporting
27 good infant feeding to promote child survival. HIV-free survival could be achieved, even

1 in rural settings, if strategies to reduce the risk of postnatal infection such as HAART to
2 breastfeeding mothers are demonstrated to be effective and feasible at scale.

3
4 In this study, amongst infants that never became infected, early feeding practices did not
5 influence long term survival. As in previous analyses of this cohort(1), numbers of infants
6 in the mixed feeding categories in the first 6 months were too small to make statistical
7 comparisons regarding transmission, including the risk of mixed feeding in the first 6
8 months versus the risk of receiving breastmilk and complementary feeds beyond 6
9 months. The overall estimated risk exposure for breastfeeding over the 18 month period
10 (9.1 cases per 100 child-years of breastfeeding) was similar to previous estimates(26).

11 Among the infants breastfed beyond 6 months of age and allowing for maternal CD4
12 counts, although the differences in overall probability of HIV-free survival between 7-18
13 months did not reach statistical significance, those who were exclusively breastfed in the
14 first 6 months tended to do better than those mixed-fed.

15
16 Maternal health remained a major determinant of HIV infections and mortality of exposed
17 infants throughout the 18 month period. Overall, the probability of HIV infection or death
18 was highest amongst infants born to mothers with low antenatal CD4 counts but also
19 significantly higher if the mother was unemployed antenatally. Unemployment could
20 represent several independent influences including dependency and lack of autonomy to
21 make choices about infant feeding practices, impaired nutrition and lack of resources e.g.
22 taxi fares to access to health services. Low birth-weight of exposed infants also
23 increased the likelihood of adverse outcomes in early life and may similarly reflect poor
24 maternal health and antenatal care. Perhaps surprisingly, infant outcomes between 7
25 and 18 months were more substantially determined by these maternal factors than by
26 feeding practices.

27

1 We were surprised by the relatively large number of mothers who continued to
2 breastfeed beyond 6 months, despite counselling, planning and access to replacement
3 feeds. That so many mothers opted to continue breastfeeding likely reflects the socio-
4 demographics of the study population and cultural issues within the communities. These
5 mothers presumably weighed up the complexities and relative inconvenience of safe
6 replacement feeding and decided that continued breastfeeding was still preferable.
7 PMTCT programmes need to offer better counselling and support throughout this time if
8 overall child health and survival are to improve.

9
10 Methodologically, we did not permit any lapses whatsoever when allocating infants to
11 specific feeding practices. If an infant received water, non-human milk or solids even for
12 one day, the infant was reclassified as mixed feeding. In comparison with our analysis of
13 HIV transmission in the first 6 months(1), in which we permitted up to 3 lapsed days
14 before exclusion to another category, this approach significantly reduced the number of
15 infants within the exclusive breastfeeding group. Also, because in this analysis we were
16 interested in transmission and survival by initial feeding mode, or feeding mode up to a
17 certain age, we did not censor when the child dropped out of the initial feeding mode.

18
19 The question remains how best to identify and support the optimal infant feeding strategy
20 beyond 6 months for individual HIV-infected women. Any approach must consider a
21 mother's prevailing or changing household circumstances as well as her own disease
22 status, to determine if, or when she should stop breastfeeding. Programmes need to
23 remain in contact with mothers to assist with the process of stopping breastfeeding and
24 offer advice on complementary feeding. Amidst the many difficult contextual issues
25 remains the greatest opportunity, namely to identify the women with low CD4 counts and
26 start them on HAART for life. Where HAART is not available for this group of women, the
27 balance of evidence suggests that where possible and safe, stopping breastfeeding at 6

1 months or before will increase the child's long term prospects of survival. The ability of
2 international recommendations, national policies, individual programmes and community
3 responses to promote and protect the equality and autonomy of women and mothers, to
4 benefit from employment and access to health interventions, will be measured by the
5 most tangible of child health outcomes, namely whether they live or die.
6

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2

3 Authors contributions

4 Nigel Rollins Design, implementation and project management of the
5 study, analysis of data and drafted manuscript

6 Renaud Becquet Analysis of data and drafted manuscript

7 Ruth Bland Design, implementation and project management of the
8 study, analysis of data and reviewed manuscript

9 Anna Coutsooudis Conceptualisation, design and implementation of the
10 study, and drafted the manuscript

11 Hoosen Coovadia Conceptualisation, design and implementation of the
12 study, and drafted the manuscript

13 Marie-Louise Newell Design of study, analysis of data and drafted manuscript

14

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13

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1 **Table 1.** Cohort profile.

2

Pregnant women enrolled	3,445
<i>Exclusion of women not infected with HIV-1 or HIV-1 status not confirmed</i>	1,679
<i>Exclusion of HIV-1 infected women lost to follow-up or dead before delivery or who had spontaneous abortion</i>	306
HIV-1 infected women having delivered	1,460
Birth outcomes	1,496
<i>Exclusion of second/third born of twins/triplets</i>	36
<i>Exclusion of stillbirths</i>	60
Single or first births, live born infants from HIV-infected mother	1,400
<i>Exclusion of infants lost to follow-up immediately after birth</i>	82
<i>Exclusion of infants not tested for HIV infection</i>	125
Mother-infant pairs included in the 18 months outcomes analyses according to infant feeding practices implemented at birth	1,193
<i>Exclusion of infants HIV-infected in peri-partum or with unknown timing of HIV-infection</i>	173
<i>Exclusion of infants dead by 3 months of age</i>	12
<i>Exclusion of infants lost to follow-up by 3 months of age</i>	56
Mother-infant pairs included in the 18 months outcomes analyses according to infant feeding practices from birth until 3 months of age	952
<i>Exclusion of infants dead between 3 and 6 months of age</i>	14
<i>Exclusion of infants lost to follow-up between 3 and 6 months of age</i>	45
Mother-infant pairs included in the 18 months outcomes analyses according to infant feeding practices from birth until 6 months of age	893

3

4

Table 2. Probability of remaining free from HIV infection and death according to infant feeding practices implemented at birth (n=1,160, with information on all variables).

	Age 3	Age 6	Age 9	Age 12	Age 18
	Months	Months	Months	Months	Months
Numbers at risk	908	841	766	703	592
Probability of remaining free from HIV-infection and death (95%CI) ¹					
Exclusive Breastfeeding group (n=937)	0.82 (0.79-0.84)	0.79 (0.77-0.82)	0.78 (0.75-0.80)	0.76 (0.74-0.79)	0.75 (0.72-0.78)
Mixed feeding group (n=105)	0.84 (0.75-0.89)	0.81 (0.71-0.87)	0.81 (0.71-0.87)	0.81 (0.71-0.87)	0.79 (0.70-0.86)
Replacement feeding group (n=118)	0.85 (0.77-0.90)	0.82 (0.74-0.88)	0.81 (0.73-0.87)	0.80 (0.72-0.87)	0.80 (0.72-0.87)
Probability of survival (95%CI) ²					
Exclusive Breastfeeding group (n=937)	0.96 (0.95-0.97)	0.93 (0.91-0.94)	0.90 (0.89-0.92)	0.89 (0.86-0.90)	0.86 (0.83-0.88)
Mixed feeding group (n=105)	0.98 (0.92-0.99)	0.97 (0.91-0.99)	0.96 (0.89-0.98)	0.94 (0.86-0.97)	0.87 (0.78-0.93)
Replacement feeding group (n=118)	0.96 (0.91-0.99)	0.91 (0.84-0.95)	0.91 (0.84-0.95)	0.89 (0.81-0.93)	0.87 (0.78-0.92)

¹ Log-Rank test between the 3 groups, p=0.43

² Log-Rank test between the 3 groups, p=0.74

Note

1,193 infants were eligible for this analysis, but 33 infants had not been fed during their first 2 days of life or had missing infant feeding data and were excluded from this analysis.

1 **Table 3.** Infant feeding practices between birth and 3 or 6 months of age

2

Infant feeding modality ¹	From birth until age 3-month	From birth until age 6-month
	n (%) ²	n (%) ³
Exclusive breastfeeding	533 (56)	278 (31)
Mixed feeding	259 (27)	410 (46)
<i>breastmilk and water only</i>	71 (7)	42 (5)
<i>breastmilk plus solids</i>	32 (3)	135 (15)
<i>breastmilk plus non-human milks</i>	122 (13)	99 (11)
<i>breastmilk plus two other things</i>	34 (4)	134 (15)
Breastfeeding ceased before age 3 or 6-month	82 (9)	136 (15)
Replacement feeding (never breastfed)	78 (8)	69 (8)

3

4 ¹ According to strict WHO definitions.

5 ² Among N=952 children not HIV-infected in peri-partum, and still alive at 3 months of age.

6 ³ Among N=893 children not HIV-infected in peri-partum, and still alive at 6 months of age.

7

8

1 **Table 4.** Determinants of HIV infection or death of infants between 7 and 18 months of age,
 2 n=893

Variables	N	Univariable analysis			Multivariable analysis		
		Hazard	95% CI	p	Adjusted	95% CI	p
		Ratio			hazard		
					ratio		
Infant feeding practices							
between birth and age 6Mo							
Breastfeeding ceased before age 6Mo or replacement feeding from birth	205	1	-	0.01	1	-	0.01
Breastfeeding beyond age 6Mo	688	2.7	1.2-5.8		2.7	1.2-6.0	
Mother employed							
Yes	122	1	-	0.03	1	-	0.04
No	771	3.5	1.1-11.2		3.4	1.1-11.0	
Sex of the child							
Male	445	1	-	0.11	1	-	0.09
Female	448	0.7	0.4-1.1		0.7	0.4-1.1	
Maternal CD4 count							
≥ 200 cells/ml	767	1	-	<0.001	1	-	<0.001
< 200 cells/ml	82	3.0	1.7-5.3		3.6	2.0-6.4	
Missing	44	1.4	0.5-4.0		1.5	0.5-4.1	

Figure 1a

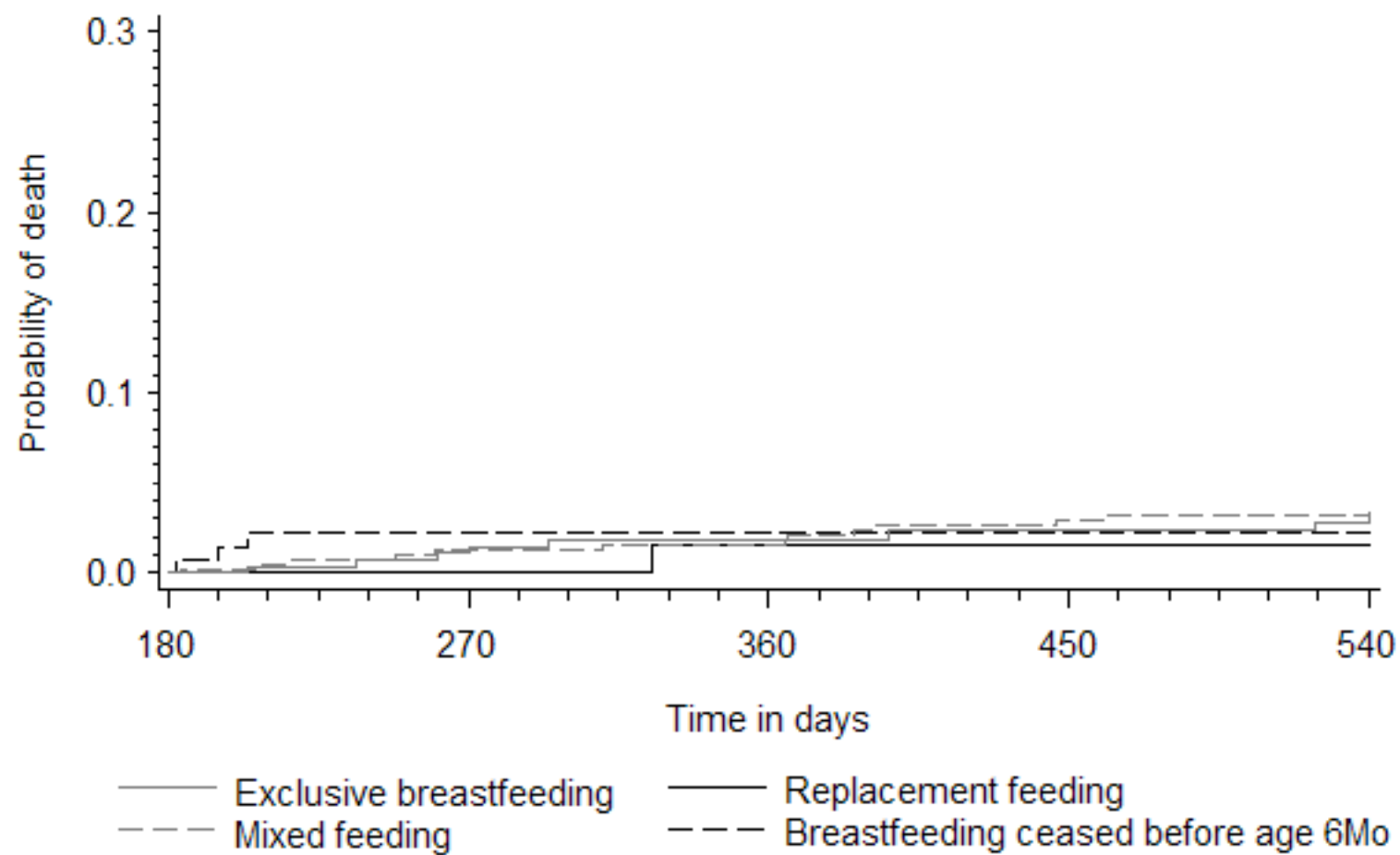


Figure 1b

