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HIV-free survival at 12 – 24 months in breastfed infants of HIV-infected women on ART

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Abstract

Objective: To provide estimates of HIV-free survival at 12-24 months in breastfed children by maternal ART (6 months or lifelong) to inform WHO HIV and Infant Feeding guidelines.

Methods: Eighteen studies published 2005-2015 were included in a systematic literature review (1295 papers identified, 156 abstracts screened, 55 full texts); papers were analysed by narrative synthesis and meta-analysis of HIV-free survival by maternal ART regimen in a random effects model. We also grouped studies by feeding modality. Study quality was assessed using a modified Newcastle-Ottawa Scale (NOS) and GRADE.

Results: The pooled estimates for 12-month HIV-free survival were 89.8% (95% confidence interval, CI: 86.5%, 93.2%) for infants of mothers on ART for 6 months postnatally (six studies) and 91.4% (95% CI 87.5%, 95.4%) for infants of mothers on lifelong ART (three studies). 18-month HIV-free survival estimates were 89.0% (95% CI 83.9%, 94.2%) with 6 months ART (five studies) and 96.1% (95% CI 92.8%, 99.0%) with lifelong ART (three studies). 24-month HIV-free survival for infants whose mothers were on ART to 6 months postnatally (two studies) was 89.2% (95% CI 79.9%, 98.5%). Heterogeneity was considerable throughout. In four studies, HIV-free survival in breastfed infants ranged from 87% (95% CI 78%, 92%) to 96% (95% CI 91%, 98%) and in formula-fed infants from 67% (95% CI 35.5%, 87.9%) to 97.6% (95% CI 93.0%, 98.2%).

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Conclusion: Our results highlight the importance of breastfeeding for infant survival and of ART in reducing the risk of mother-to-child HIV transmission and support the WHO recommendation to initiate ART for life immediately after HIV diagnosis.

Keywords: HIV-free survival, ART, women, systematic review

Introduction

The 2010 WHO infant feeding guidelines in the context of HIV infection recommended exclusive breastfeeding (EBF) for 6 months followed by complementary feeding and continued breastfeeding (CBF) for up to one year, under the cover of antiretroviral treatment (ART) to either the mother or the infant (1). However, these recommendations were based on limited evidence in terms of final HIV-free survival and also toxicity of ART to infants where the infant received prophylaxis to prevent mother-to-child transmission (PMTCT). Since then, further evidence has become available from studies and programmes where PMTCT postnatally was achieved through maternal ART or infant ARV prophylaxis, and a summary of these data could provide information for recommendations on duration of breastfeeding.

In late 2015 WHO revised HIV ART guidelines to include treatment for all immediately upon diagnosis of HIV infection(2). This systematic review was commissioned by WHO and contributed to the development of the 2015 WHO HIV Infant Feeding guidelines. We present the results from a systematic review and the associated GRADE evidence summary tables of HIV-free survival at 12, 18 and 24 months in infants born to women on ART for life or for six months postpartum and by infant feeding modality.

Methods

Our systematic review considered both experimental and observational studies, and included HIV positive mothers receiving ART and their breastfed children. Infants may also have received prophylactic ART as per WHO 2010 guidelines. Exposure was defined as HIV ART (and duration) and breastfeeding (and duration) and outcome measures were HIV-free survival and overall and postpartum HIV transmission between birth and 24 months of age.

SB, LB and MLN searched English literature from multiple electronic databases including PubMed, MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Web of Science, and CINAHL for articles published between 2005 and 2015. The search words in PubMed are shown in a footnote to Figure 1. The search terms were adapted for other databases.

Reference lists from relevant studies, grey literature and online abstracts from the International IAS AIDS Conference in Melbourne 2014 and the 2013-2015 Conferences on Retroviruses and Opportunistic Infections were also searched. Reference lists of articles identified from the search of databases and conference abstracts were scrutinised, and in cases where relevant information was not available in the publication, authors were contacted for specific additional information regarding infant feeding modality.

The quality of studies included in the analysis was assessed using a modified Newcastle-Ottawa Scale (NOS) (3, 4) (Supplementary Table 1). Although some of the included studies were nested within randomised controlled trials, randomisation was not based on the intervention of interest (breastfeeding) and these studies were considered cohorts. Each study could score a maximum of six stars on selection and four on outcome; factors considered included the representativeness of the study population, ascertainment of exposure to ART and breastfeeding, initiation on basis of ART eligibility, maternal adherence to ART and duration of breastfeeding. Ascertainment of outcome (HIV-free survival) included timing of assessment and whether the outcome was stratified by feeding, length of follow up and loss to follow up.

The information obtained from the NOS was used to comment on the quality of the included studies in GRADE with respect to study limitations/risk of bias (5). We also considered consistency of results, directness, precision and publication bias.

Synthesis of evidence

We undertook a narrative synthesis and obtained pooled estimates of HIV-free survival with a heterogeneity score based on a random effects meta-analysis in STATA 13 (Stata Corp, 2013). We also summarised the information in graphs depicting HIV-free survival rates by duration of maternal ART where possible and additionally presented HIV transmission rates for studies that provided transmission rates at 6 months and at the end of follow-up. If no confidence interval for HIV-free survival estimated was provided, it was calculated based on the number of events and those at risk using the formula described by Eayres (6).

Results

The search process identified 1295 citations, of which 1139 were excluded on the basis of being a duplicate, review, qualitative study or not evaluating transmission, mortality or HIV-free-survival (Figure 1). Abstracts of the remaining 156 studies were evaluated by SB and LC and 54 texts were se-

lected for full screening. SB, LC and MLN undertook the full text screening. Six additional articles from the references were identified through full text screening, bringing the total to 60 (Figure 1). Eighteen studies were included in the analysis. Details of excluded studies with reason are provided in Supplementary Table 2. Eight additional papers from selected studies provided additional information for the assessment of quality of studies and data collection (7-14).

We present the evidence using a narrative synthesis, in addition to providing a pooled estimate with a heterogeneity score based on a random effects meta-analysis, as recommended for use in the analysis of studies of different design (15). Of the 18 selected studies, one was performed in India and the remaining 17 were from African countries. Five studies were conducted in rural areas (16-20) and the remainder in urban areas. All 18 were cohort studies, of which 7 were nested within randomised clinical trials (see Supplementary Table 3 for full study details). Most studies were a follow-up of mothers receiving ART for prevention of mother-to-child transmission (PMTCT) (16, 18, 19, 21-25), with mothers advised to exclusively breastfeed for six months with rapid weaning thereafter, in line with the prevailing WHO recommendations. Seven studies offered lifelong ART irrespective of CD4 count and supported breastfeeding for 12 months (16, 21, 22, 25-28). Thomas et al. (29) presented findings from a clinical trial evaluating two combination ART regimen, and was included as a cohort of all women on ART postnatally. Thakwalakwa et al. (16) randomised mothers/infants postpartum to two types of complementary foods after weaning; all mothers received ART lifelong including throughout the breastfeeding period. Tonwe-Gold et al. (25) presented findings of a cohort of women who received ART for life if they were ART-eligible as per prevailing WHO guidelines or who received short-course ART for PMTCT only; data are included accordingly.

The 7 cohorts nested within clinical trials evaluated the use of ART during pregnancy and postnatally in reducing mother-to-child transmission (MTCT) of HIV and infant deaths (8, 16, 28-32). Counil et al. (8) in the Kesho Bora study compared ART through 6 months of breastfeeding with short duration of peri-partum ART, and presented HIV-free survival in children who were never breastfed and those who were breastfed for more than three months. Jamieson et al. (32) and Coovadia et al. (30) compared rates and risk by prolonged infant nevirapine prophylaxis, with mothers on different types of ART, but provided separate estimates on HIV-free survival for the group of mothers on ART for at least 6 months.

Quality of studies

Supplementary Table 4 presents findings of the assessment of the quality of the studies based on the modified Newcastle-Ottawa Scale. The study by Ngoma et al. (27) had the highest quality in terms of selection (six stars), followed by Sagay et al. et al. (26), Cohan et al. (28), Jamieson et al. (32), Thomas et al. (29) and Peltier et al. (20), all with 4 stars. The studies by Alvarez-Uria et al. (17) and Tonwe-Gold et al. (25) scored highest on quality of outcome assessment (4 stars).

Most studies did not provide details on type of feeding, and assumed (but did not formally document) that most mothers exclusively breastfed up to 5 or 6 months as recommended. Estimates of HIV-free survival by type of feeding could only be obtained from 4 studies (8, 17, 20, 33). Tonwe-Gold (25) presented information on HIV transmission by feeding type and Cournil et al. (8) presented rates in children who were either formula-fed from birth, breastfed for less than 3 months or for 3 months or longer. Three studies compared transmission or death between breastfed and formula-fed infants (17, 20, 33).

Eleven studies provided HIV-free survival or rates of transmission and mortality from birth (18, 19, 23-29, 31, 32). Other studies excluded deaths and HIV transmission in the first days or weeks of life and provided only postnatal rates.

HIV-free survival

At age 12 months

Estimates of 12-month HIV-free survival, with confidence intervals, for breastfed infants by duration of maternal ART were obtained from 10 studies (Figure 2). In 6 studies (Group 1 in Figure 2), HIV-free survival was reported for infants whose mothers were on ART up to 6 months postnatally only, with 12-month estimates ranging from 85% (95% CI 74.6%- 91.7%) (18) to 96% (95% CI 91%-98%) (17). The pooled estimated 12-month HIV-free survival was 89.8% (95% CI 86.4%-93.2%), with considerable heterogeneity ($I^2=83.1\%$).

In three studies, 12-month HIV-free survival was estimated amongst infants whose mothers were on lifelong ART (Group 2 in Figure 2) with estimated HIV-free survival ranging from 88.8% (95% CI 82.6%-95%) (25) to 95% (95% CI 92%-97%) (28). The pooled estimate of 12-month HIV-free survival was 91.8% (95% CI 87.7%-95.9%); heterogeneity was considerable ($I^2=71.5\%$).

The study by Giuliano (22) (Group 3 in Figure 2), with an estimate of 86.6% (95% CI 82.4%- 90.7%) included some mothers on ART up to 6 months postnatally only and others on lifelong ART, but separate estimates were not provided.

At age 18 months

Eight studies provided estimates for 18-month HIV-free survival (Figure 3), by duration of maternal ART. In the 5 studies reporting HIV-free survival at this age for infants of women who were on ART up to 6 months postnatally only (Group 1 in Figure 3), HIV-free survival ranged from 81.6% (95% CI 73.4%-87.7%)(19) to 95.2% (95% CI 93.2%-97.3%) (10). The pooled estimate of 18-month HIV-free survival for this group was 89.0% (95% CI 83.9%- 94.2%), with considerable heterogeneity ($I^2= 91.7\%$).

In studies where women were on lifelong ART (Group 2 in Figure 3), 18-month HIV-free survival estimates ranged from 87.2% (95% CI 79.2%-92.5%) (27) to 97.6% (95% CI 96.7%-98.6%) (26). The pooled estimated of 18-month HIV-free survival for this group was 96.1% (95% CI 93.0%-99.2%), again with considerable heterogeneity ($I^2= 78.5\%$).

At age 24 months

Twenty-four-month HV-free survival estimates from 3 studies are shown in Figure 4. The estimates in the 2 studies that reported HIV-free survival amongst children whose mothers were on ART up to 6 months postnatally only (Group 1 in Figure 4) were 84.3% (95% CI 80.6%-87.3%) (29) and 93.8.0% (95% CI 92.9%-96.5%) (31). The pooled estimate for HIV-free survival at 24 months was 89.2% (95% CI 79.9%-98.5%); heterogeneity was considerable ($I^2= 95.8\%$).

In the study by Giuliano et al. (22), (Group 2 in Figure 4) estimated HIV-free survival at 24 months was 85.8% (95% CI 81.4% 90.1%), based on a mixed group of infants with respect to mother's ART, some were on ART up to 6 months postnatally only, while others were on ART for life.

At 12, 18 and 24 months

Three studies provided estimates of HIV-free survival at 12, 18 and 24 months allowing a comparison of HIV-free survival between 12 and 24 months (22, 23, 29). In all 3, HIV-free survival at 18 months and/or 24 months was not statistically significantly different from the estimate at 12 months. HIV-free survival estimates were 86.6% (95% CI 82.4%, 90.7%) and 85.8% (95% CI 81.4, 90.1%) at 12 and 24 months respectively in Giuliano et al. (22), 86.5% (95% CI 83.1%, 89.3%), 84.7% (95% CI 80.6%, 87.7%) and 84.3% (95% CI 80.6%, 87.3%) at 12, 18 and 24 months respectively in Thomas et al. (29)

and in Kilewo et al. (23) the estimates were 87.2% (95% CI 84%, 90.4%) at 12 months and 86.4% (95% CI 83.1%, 89.7%) at 18 months.

HIV-free survival by infant feeding modality

In the Kesho Bora study (8, 9), estimated 18-month HIV-free survival was statistically significantly higher among formula-fed (97.6%; 95% CI 93%, 98%) than infants breastfed for less than 3 months (87%; 95% CI 78%, 92%) (Figure 5). The difference between formula-fed infants (97.6%; 95% CI 93%, 98%) and those breastfed for more than 3 months (95%; 95% CI 91%, 97%) was not statistically significant. In the studies by Alvarez-Uria (17), reporting estimates at 18 months, Homsy et al (19) at 12 months and Peltier et al. (20) at 9 months differences in HIV-free survival between formula-fed and breastfed infants were not statistically significant (Figure 5).

HIV Transmission

Eight studies provided estimates of death and transmission overall and after 6 months of age, when the infant would have been weaned and mothers were no longer receiving ART. In Ngoma et al. (27) there were 3 peripartum infections, none between 6 weeks and 6 months, and 6 after 6 months. In the studies of both Giuliano et al. (22) and Kilewo et al. (23), there were 8 infections overall, 4 before weaning at 6 months and 4 after weaning. In Giuliano et al. 2 of the 4 mothers who transmitted HIV after weaning were still receiving ART. In the other 5 studies there were fewer infections after 6 months of age than before (8, 24, 26, 29, 32) but numbers were again very limited.

Mortality

The pattern of infant deaths before and after weaning varied across studies. Jamieson et al. (32) reported the same number of deaths before and after weaning (9 of 18 deaths before weaning); Tonwe-Gold (25) reported 1 death after and 9 deaths before weaning and Ngoma et al (27) reported 8 of 20 deaths after weaning. Thomas et al. (29), Shapiro et al. (31), Kilewo et al.(23) and Marazzi et al.(24) reported higher numbers of deaths after (31 of 49, 22 of 37, 21 of 31 and 7 of 11 respectively) than before weaning. In Shapiro (31), the death rate within 3 months of weaning was significantly higher than during breastfeeding (RR 3.7; 95% CI: 1.3-12.0; p=0.007), and the same was shown comparing those who were weaned before 3 months of age and those aged 3 months or more at weaning (RR=7.5; 95% CI: 3.2-18.4; p < 0.001). Cournil et al. (8) did not report any deaths after 6 months, but the risk of dying by 6 months of age in children who stopped breastfeeding before 3 months of age was higher than in those who stopped after more than 3 months (HR 3.94; 95% CI: 1.27-12.27).

GRADE profile

An evaluation of the overall quality of the combined studies for each outcome is provided in Supplementary Table 5 using the GRADE approach (5). Study limitations were based on the assessment from the Newcastle-Ottawa Scale and combined with an evaluation of inconsistency, indirectness, imprecision and publication bias. All studies were observational and initially scored as low quality; they were further downgraded for indirectness because their research areas were not directly in line with the research question. Where a pooled analysis was undertaken and a pooled estimate provided, studies were further downgraded for inconsistency when heterogeneity could not be explained. In all groups of studies there was at least one study with a risk of bias pertaining to lack of detailed information on feeding leading to further downgrading. In one study, the criteria for assessing HIV-free survival were not clear (21) and this contributed to the downgrading of the quality of the studies grouped together with this study. One study (22) was not downgraded for risk of bias and inconsistency, as it was the single study contributing data in that group.

Discussion

This systematic review confirms substantially reduced rates of overall and postnatal HIV transmission and mortality up to 24 months of age when pregnant and breastfeeding women receive ART. The difference in HIV-free survival between infants of mothers receiving ART for PMTCT only or for life diverged beyond 6 months post-delivery and became particularly evident at 18 months. At this time-point the estimated HIV-free survival was about 89% when mothers ceased ART at 6 months, and 96% when mothers continued ART for life. The risk of transmission through breastfeeding continued beyond the recommended 6 months and after cessation of maternal ART (1).

Our results thus confirm the importance of breastfeeding for infant survival and the effectiveness of ART in reducing the risk of mother-to-child HIV transmission. In most studies (5 of 8) there were more infant deaths after weaning than before, but in only 1 of 8 studies was the number of HIV transmissions after 6 months higher than before, which together would suggest that HIV-free survival in the first year of life is substantially affected by increased mortality following early cessation of breastfeeding rather than by increased infections that may occur in infants of women who had stopped taking ART (8, 22-25, 27, 29, 31, 32).

Our review, although systematic in nature, had limitations. There was considerable statistical heterogeneity in all pooled estimates, and the overall assessment of quality of the evidence was very low. The low quality of evidence was mainly attributed to the fact that all studies in-

cluded in the analysis were observational and the evidence was further downgraded due to indirectness, and lack of data on feeding history and adherence to ART. The absolute estimates of HIV-free survival should thus be interpreted with caution, and consider both the mean value and the confidence interval limits. Further, we were unable to formally allow for factors known to be associated with transmission and/or child survival, and heterogeneity between studies could be partially due to differences in other factors associated with child mortality. There was limited information on children born to women on lifelong ART where ART was initiated before advanced HIV progression, and most of the women on lifelong ART in the studies that reported such information would have been eligible as per the national and WHO guidelines at the time of the study (16, 21, 25-28).

Increased HIV-free survival in the studied populations was linked to early initiation of maternal ART in pregnancy, continued postpartum, and breastfeeding. Increased infant/child mortality after six months of life may be attributed to early cessation of breastfeeding and could possibly contribute to reduced HIV-free survival in non-breastfed HIV-exposed infants. Recent findings from a randomised trial, evaluating the use of two different infant antiviral drugs in the prevention of post-natal HIV acquisition, showed HIV-free survival similar to what we present here with maternal ART (34); infant ARV may therefore be an alternative intervention to achieve the prevention of mother to child transmission in cases where maternal ART is not possible or not being adhered to. Our findings suggest prolonged breastfeeding for women on ART for life is beneficial in terms of HIV-free survival at least up to 2 years of age. With expanding eligibility criteria, and WHO now recommending initiation of ART for life immediately after HIV diagnosis, most women will be on ART for life from before or early pregnancy.

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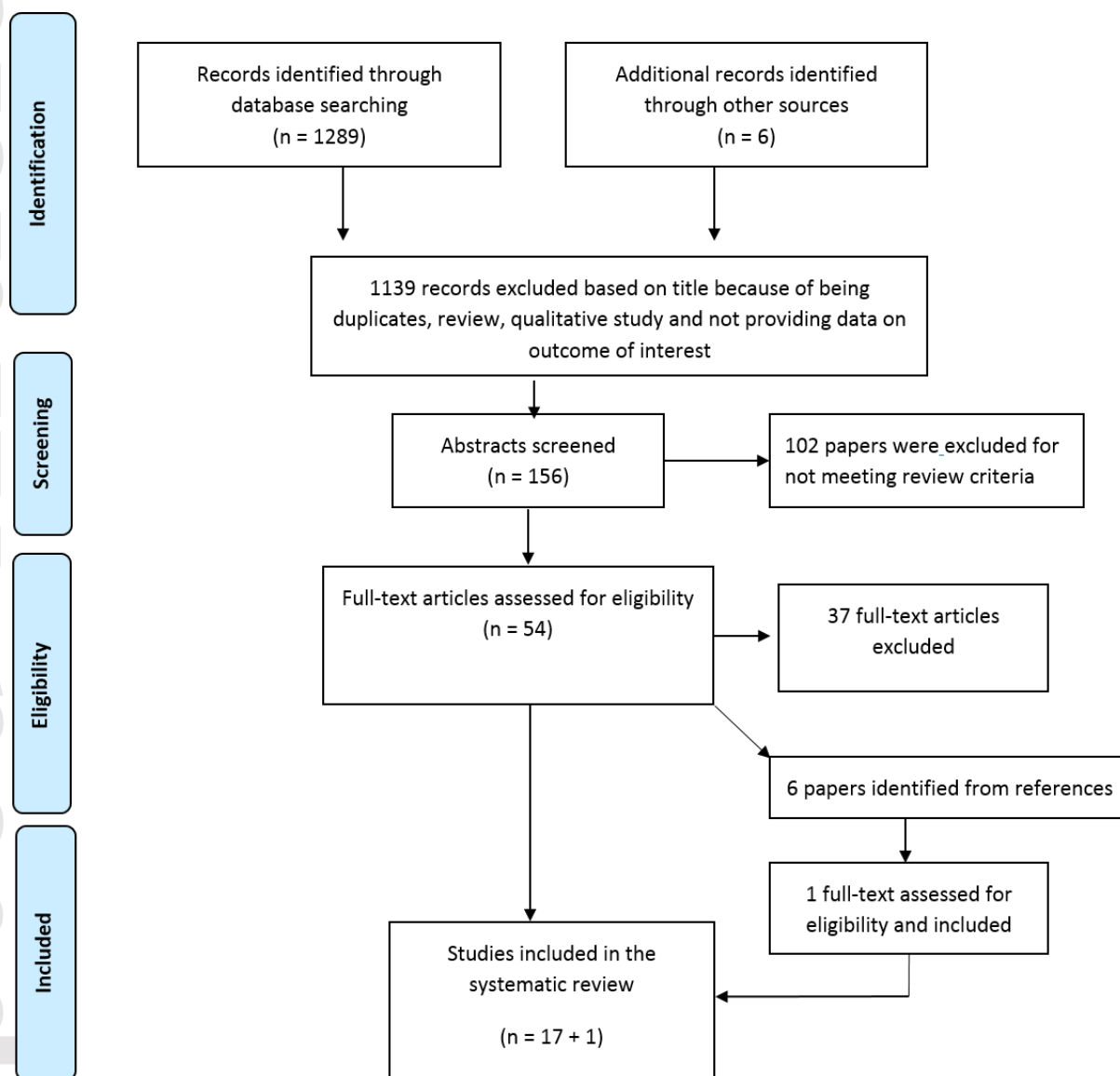
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Figure 1. Flowchart of screening process



Search Terms in PubMed (((*Maternal[Title/Abstract] OR mother*[Title/Abstract]*) AND (*Antiretroviral therapy[Title/Abstract] OR Antiretroviral*[Title/Abstract] OR ART[Title/Abstract] OR ARV[Title/Abstract] OR HAART[Title/Abstract]*) AND (*HIV free survival[Title/Abstract] OR HIV[Title/Abstract] OR Transmi*[Title/Abstract] OR Death[Title/Abstract] OR Mortality[Title/Abstract]*) AND (*Breastfeeding[Title/Abstract] OR Postnatal[Title/Abstract] OR Breast*[Title/Abstract]*)) AND ("2005"[Publication Date] : "2015"[Publication Date])).

Figure 2. 12-Month HIV-free Survival

- Group 1: Mothers on ART up to six months postnatally
- Group 2: Mothers on Lifelong ART
- Group 3: Mixture of Lifelong ART and ART up to six months postnatally

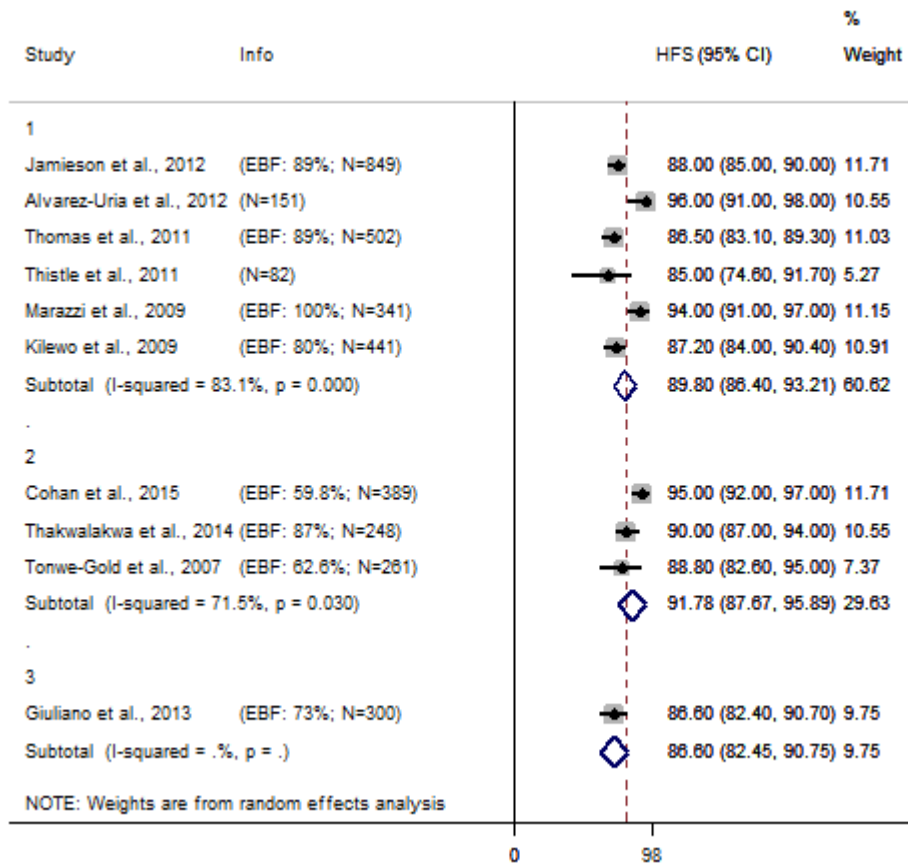


Figure 3. 18-Month HIV-free survival in children whose mothers breastfed and were on ART

- Group 1: Mothers on ART up to six months postnatally only
- Group 2: Mothers on lifelong ART

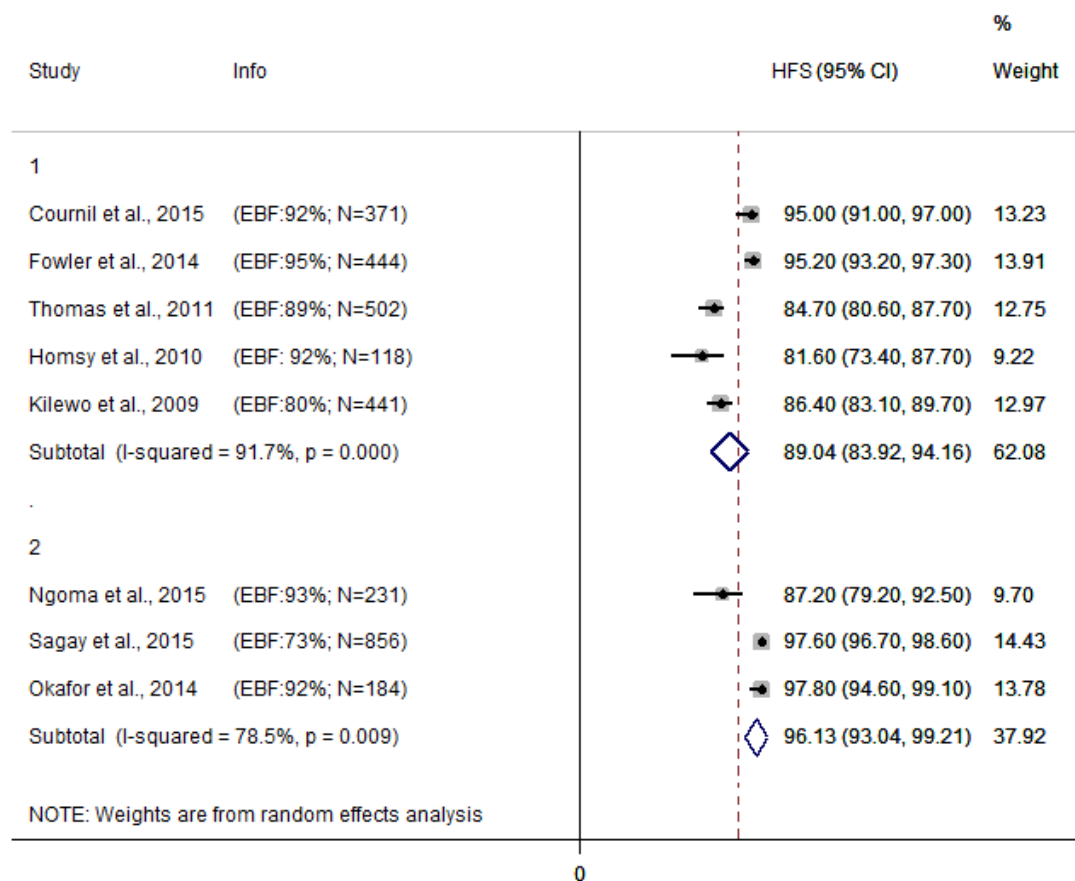


Figure 4. 24-Month HIV-free survival in children whose mothers breastfed and were on ART.

- Group 1: Mothers on ART up to six months postnatally
- Group 2: Mixture of mothers, some on lifelong ART, others on ART to six months postnatally

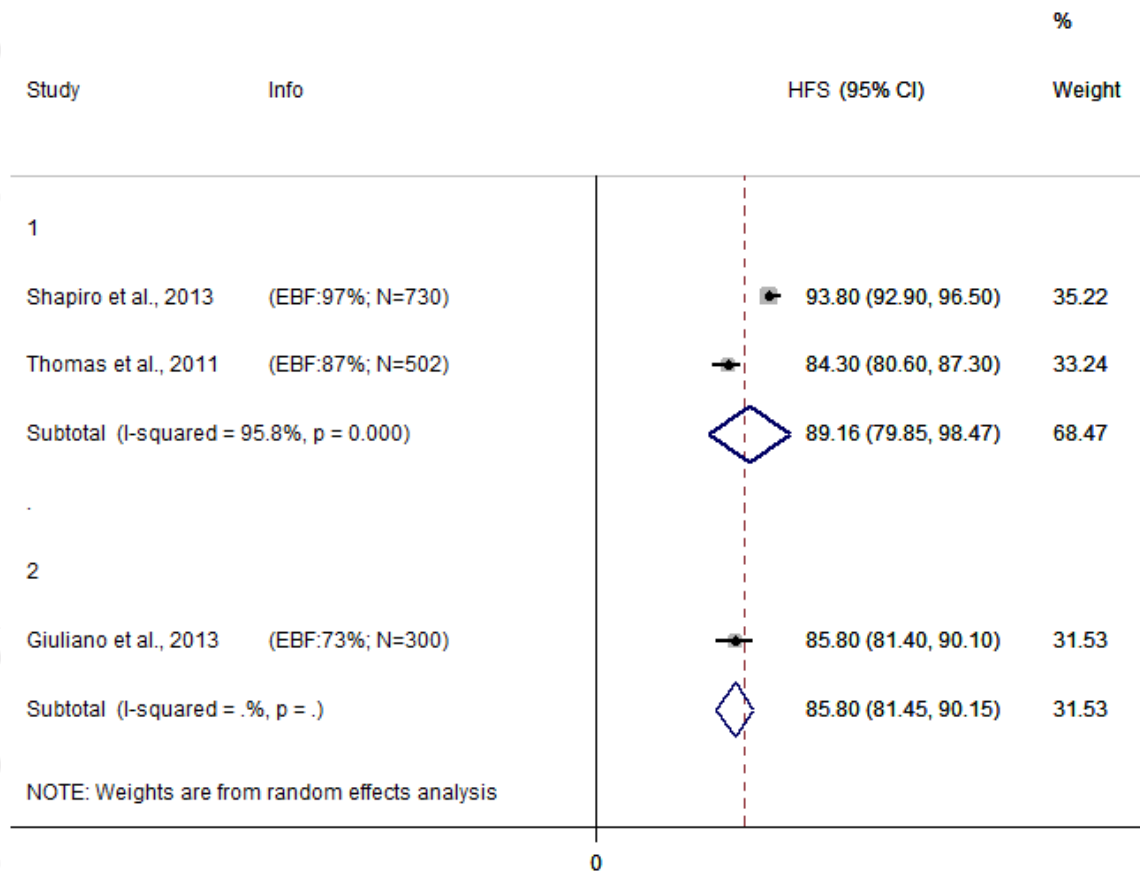
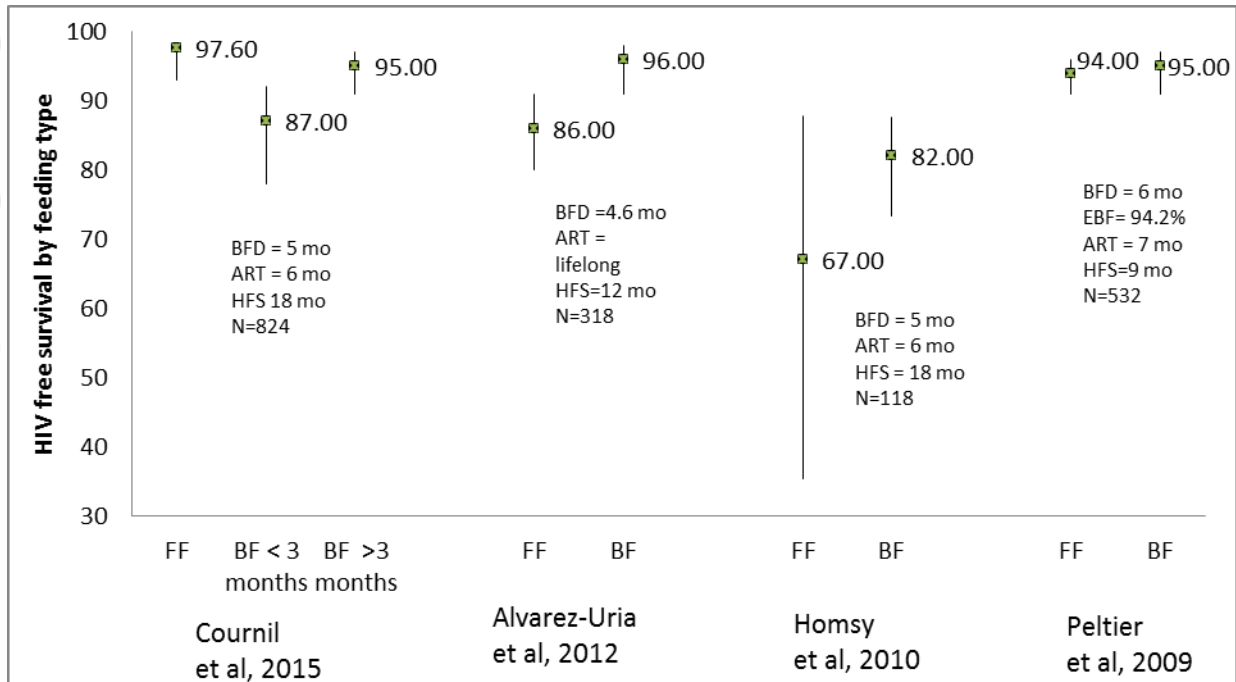


Figure 5. HIV-free survival by feeding modality in four studies



Notes: FF: Formula fed, BF: Breastfed

1. Counil *et al.*, 2015 excluded mothers in clinical stage 4 or with CD4 <200 cells/mm³. HIV-free survival excluded endpoints during the first 2 weeks, and was measured at 18 months.
2. Alvarez Uria *et al.*, 2012: HIV free survival was obtained after 8 weeks, and measured at 12 months.
3. Homsy *et al.*, 2010: Mothers received ART when CD4 cell counts ≤ 250 cells/ μ L or when with WHO stage III or IV disease. There was no transmission in the study, but 4 children who died had not been tested. HIV-free survival was not provided according to feeding modality, but numbers of deaths by feeding were provided. Among 118 children, only 9 were formula fed, of whom 3 died; 2 received mixed feeding, and both died.
4. Peltier *et al.*, 2009: Mothers with CD4 cell counts ≤ 350 cells/mm³ remained on ART. HIV free survival was measured at 9 months and endpoints were considered from 24 hours.