A review of clinical trials to prevent mother-to-child HIV-1 transmission in Africa and inform rational intervention strategies

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Authors' objectives
To assess whether antiretroviral therapy or infant feeding interventions are effective in reducing the risk of mother-to-child human immunodeficiency virus (HIV)-1 transmission in breast-feeding African populations.

Searching
MEDLINE, AIDSLine and the International HIV Conference database were searched (search terms provided). A further search was conducted using the authors' names from the studies identified.

Study selection
Study designs of evaluations included in the review
Only randomised controlled trials (RCTs) were included in the review.

Specific interventions included in the review
Antiretroviral and infant feeding interventions were eligible for inclusion in the review. The antiretroviral therapies evaluated in the included studies were: zidovudine (ZDV) monotherapy, nevirapine (NVP) monotherapy and ZDV-lamivudine combination therapy (ZDV-3TC).

The dosage, timing and frequency of administration of the antiretrovirals varied and included administration in the antenatal, intrapartum and postpartum periods (for mother and/or child) as either a single dose, twice daily or at specific time intervals throughout a 24-hour period.

The infant feeding intervention compared breast-feeding with formula feeding.

Participants included in the review
Breast-feeding African populations were eligible for inclusion. The participants in the included studies were pregnant women with HIV-1 infection in Africa.

Outcomes assessed in the review
The outcomes of interest were HIV-1 transmission rates and mortality.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

Where available, data were extracted for point estimates of HIV-1 transmission, cumulative transmission and mortality, then used to determine the relative efficacy of the intervention to reduce early and late transmission and increase HIV-free survival. Relative efficacy was obtained by calculating the preventive fraction (PF), which was the proportion of potential cases of mother-to-child HIV-1 transmission that could be prevented by providing the intervention to HIV-positive pregnant women. Additional information relating to factors associated with HIV-1 transmission were extracted.
These included the duration and proportion of participants breast-feeding, the duration of membrane rupture and the mode of delivery.

**Methods of synthesis**

How were the studies combined?
The studies were presented in a narrative discussion.

How were differences between studies investigated?
Differences between the studies were explored though the graphical display of trial results and the tabulation of characteristics of the trial populations.

**Results of the review**

Six RCTs were included in the review. Five evaluated antiretroviral therapy (n=4,088) and one evaluated infant feeding (n=425).

**ZDV monotherapy.**

Two pooled trials (n=711) evaluated the antenatal, intrapartum and postpartum administration of ZDV to the mother in comparison with placebo. The results suggested that, compared with placebo, ZDV prevents 41% of early HIV-1 transmission cases (PF 41%, 95% confidence interval, CI: 17, 58, P<0.05). The cumulative HIV-1 transmission rates suggest that at 2 years ZDV prevented 26% of HIV-1 transmission cases in comparison with placebo (PF 26%, 95% CI: 2, 44).

**NVP versus ZDV.**

One trial (n=619) evaluated intrapartum and postpartum (to the child) administration of NVP versus ZDV. The results suggested that, compared with ZDV, NVP prevents 42% of early HIV-1 transmission (PF 42%, 95% CI: 13, 62, P=0.0063). At 18 months, the cumulative HIV-1 transmission rates suggested NVP prevented 41% of cases of late HIV-1 transmission in comparison with ZDV (PF 41%, 95% CI: 16, 59). In addition, HIV-free survival was significantly higher for those who had received NVP (79.3%) than for those who had received ZDV (69.3%), (P=0.0048).

**Combination therapy.**

One placebo-controlled trial (n=1,457) found a statistically significantly higher proportion of cases of early HIV-1 transmission prevented following the antenatal, intrapartum and postpartum administration of ZDV-3TC to both mother and child (PF 63%; P=0.001), or the intrapartum and postpartum administration to both mother and child (PF 42%; P=0.025). However, there was no significant difference in the cases prevented following only intrapartum administration of ZDV-3TC, compared with placebo (PF 7%; P=0.74; calculated from data derived from the graph). At 18 months, there was no significant difference in HIV-free survival for any of the treatment groups in comparison with placebo.

**Combination therapy versus NVP.**

One trial (n=1,301) compared the intrapartum and postpartum administration of ZDV-3TC versus NVP to mother and child. The results suggested that NVP prevents 23% of the cases of early HIV-1 transmission in comparison with ZDV-3TC (PF 23%; P>0.05; calculated from data derived from the graph).

**Infant feeding.**

The use of feeding formula was associated with the prevention of 51% of the cases of early HIV-1 transmission, compared with breast-feeding (PF 51%; P=0.005). Furthermore, the use of formula was associated with a higher probability of HIV-free survival for 2 years in comparison with breast-feeding (70% versus 58%; P=0.01). However, the cumulative death rate was high in both groups.
Between the studies, there was a substantial difference in the key risk factors associated with mother-to-child transmission of HIV-1. The initiation of breast-feeding ranged from 40 to 100% in the studies evaluating antiretroviral therapy, with a median breast-feeding time ranging from 9 to 18 months. In the breast-feeding study, 30% of women assigned to the formula group were non-compliant and breast-fed. The proportion of study participants who received a Caesarean also varied significantly (from 1.5 to 32%).

**Authors' conclusions**
The authors' conclusions appear to be that short (intrapartum and one-week postpartum) administration of NVP or ZDV-3TC significantly reduces perinatal HIV-1 in African populations.

**CRD commentary**
The review addressed a clear question. However, the absence of explicit inclusion criteria, combined with no details of the methods used to select the primary studies and extract the data, suggest that selection and observer bias in the review process cannot be ruled out. The search for studies was specific to the subject area and included a search for unpublished work. However, there was no mention as to whether the search was limited to articles published in the English language, so the risk of publication bias cannot be ruled out. Relevant details of the primary studies were presented in tabular and graphical format, though the results were not easy to interpret. A narrative review was appropriate due to the significant heterogeneity, although a systematic assessment of the quality of the evidence was not performed.

Given the variations in comparator group, heterogeneity between the studies and the methodological flaws of this review, it is difficult to confidently determine the efficacy of the antiretroviral regimes included in this review. It would therefore appear that the authors' conclusions are unclear and should be treated with caution.

**Implications of the review for practice and research**
Practice: The authors stated that efforts to decrease mother-to-child transmission of HIV-1 and promote child survival should combine breast milk replacement and earlier weaning with effective antiretroviral regimens.

Research: The authors stated that future clinical trials should evaluate the safety and efficacy of potent antiretrovirals regimens to suppress viral load post-delivery and reduce early HIV-1 transmission.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.