# Extended pre-exposure prophylaxis with lopinavir–ritonavir versus lamivudine to prevent HIV-1 transmission through breastfeeding up to 50 weeks in infants in Africa (ANRS 12174): a randomised controlled trial

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## Summary

**Background** **Strategies to prevent postnatal mother-to-child transmission of HIV-1 in Africa, including infant prophylaxis, have never been assessed past 6 months of breastfeeding, despite breastfeeding being recommended up to 12 months after birth. We aimed to compare the efficacy and safety of infant prophylaxis with the two drug regimens (lamivudine or lopinavir–ritonavir) to prevent postnatal HIV-1 transmission up to 50 weeks of breastfeeding.**

**Methods** **We did a randomised controlled trial in four sites in Burkina Faso, South Africa, Uganda, and Zambia in children born to HIV-1-infected mothers not eligible for antiretroviral therapy (CD4 count >350 cells per µL). An independent researcher electronically generated a randomisation schedule; we then used sequentially numbered envelopes to randomly assign (1:1) HIV-1-uninfected breastfed infants aged 7 days to either lopinavir–ritonavir or lamivudine (paediatric liquid formulations, twice a day) up to 1 week after complete cessation of breastfeeding or at the final visit at week 50. We stratified the randomisation by country and used permuted blocks of four and six. We used a study label on drug bottles to mask participants, study physicians, and assessors to the treatment allocation. The primary outcome was infant HIV-1 infection between age 7 days and 50 weeks, diagnosed every 3 months with HIV-1 DNA PCR, in the modified intention-to-treat population (all who attended at least one follow-up visit). This trial is registered with ClinicalTrials.gov, number NCT00640263.**

**Findings** **Between Nov 16, 2009, and May 7, 2012, we enrolled and randomised 1273 infants and analysed 1236; 615 assigned to lopinavir–ritonavir or 621 assigned to lamivudine. 17 HIV-1 infections were diagnosed in the study period (eight in the lopinavir–ritonavir group and nine in the lamivudine group), resulting in cumulative HIV-1 infection of 1·4% (95% CI 0·4–2·5) and 1·5% (0·7–2·5), respectively. Infection rates did not differ between the two drug regimens (hazard ratio [HR] of lopinavir–ritonavir versus lamivudine of 0·90, 95% CI 0·35–2·34; p=0·83). Clinical and biological severe adverse events did not differ between groups; 251 (51%) infants had a grade 3–4 event in the lopinavir–ritonavir group compared with 246 (50%) in the lamivudine group.**

**Interpretation** **Infant HIV-1 prophylaxis with lopinavir–ritonavir was not superior to lamivudine and both drugs led to very low rates of HIV-1 postnatal transmission for up to 50 weeks of breastfeeding. Infant pre-exposure prophylaxis should be extended until the end of HIV-1 exposure and mothers should be informed about the persistent risk of transmission throughout breastfeeding.**

**Funding** **INSERM/National Agency for Research on AIDS and Viral Hepatitis (including funds from the Total Foundation), European Developing Countries Clinical Trials Partnership, Research Council of Norway.**

## Introduction

Breastfeeding remains an important barrier to the prevention of mother-to-child transmission of HIV-1.[1] Similar to adult sexual transmission of HIV, two approaches can be used to prevent acquisition through breastfeeding: to reduce infectiousness through treatment of the infected individual (maternal antiretroviral therapy [ART]; WHO option B) or to give antiretroviral prophylaxis to the uninfected individual (pre-exposure prophylaxis [PreP] of infants; WHO option A).[2]

Infant PreP (with either nevirapine or lamivudine)[3–9] and maternal ART have both shown efficacy in trials,[3,10–13] but no study regimen has been assessed for longer than 6 months of infant exposure, even though the current recommended duration of breastfeeding is 12 months. Although nevirapine is widely used for infant prophylaxis, failures can cause viral resistance, preventing the use of any non-nucleoside reverse transcriptase inhibitors to treat the infected child. Lamivudine seems to have similar efficacy and safety until 6 months, as does nevirapine, and failures less restrict later treatment choices.

Published **Online** November 18, 2015 http://dx.doi.org/10.1016/S0140-6736(15)00984-8

See **Online/Comment** http://dx.doi.org/10.1016/S0140-6736(15)00983-6

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See Online for appendix

## Research in context

### Evidence before this study

We searched PubMed for clinical trial or cohort reports about prophylactic prevention of HIV-1 breastfeeding transmission published in English before Aug 1, 2012, with the following keywords "prevention of breastfeeding transmission of HIV-1" and "randomised clinical trial" or "cohort study". We found four clinical trial reports (SWEN, PEPI, HTPN 046, and BAN) and one intervention cohort (MITRA) on infant prophylaxis and two randomised trials for maternal antiretroviral prophylaxis (Kesho Bora and BAN) and two cohort studies (KBS and Amata). All studies involved prophylaxis for a maximum of the first 6 months of the baby's life. None covered the entire recommended period of breastfeeding (12 months). These studies showed that once prophylaxis is interrupted, if the baby's exposure is maintained, transmission risk returned to the same as without prophylaxis.

### Added value of this study

Lopinavir–ritonavir was not superior to lamivudine and both drugs were equally effective in reducing the risk of HIV-1 transmission. Transmission risk after 6 months was similar to that before this time.

### Implications of all the available evidence

Infant prophylaxis during 12 months is a safe and efficient strategy that should be considered to reduce HIV-1 residual transmission during maternal antiretroviral therapy (ART), when mothers are not ready to start ART during pregnancy, or when countries cannot implement universal maternal ART.

Lopinavir–ritonavir, a protease inhibitor with a paediatric formulation available, has a greater antiviral activity and a higher genetic barrier to HIV-1 drug resistance than do nucleosidic or non-nucleosidic reverse transcriptase inhibitors.[14] The regimen also has a good safety profile in young children,[14–16] which makes this drug a good candidate for prophylactic purposes.

We aimed to compare lopinavir–ritonavir with lamivudine (given from day 7 after birth until either 50 weeks or 1 week after cessation of breastfeeding) on the rate of HIV-1 transmission and adverse events among HIV-1-exposed infants in Africa.

## Methods

### Study design and participants

ANRS 12174 is a randomised controlled trial including HIV-infected pregnant women identified at antenatal clinics at four African sites: Ouagadougou University Teaching Hospital (urban site in Burkina Faso), East London Hospital Complex (urban site in South Africa); Mbale Regional Referral Hospital (semi-rural site in Uganda), and Lusaka University Teaching Hospital (urban site in Zambia). The study protocol is detailed elsewhere.[17]

Mothers and infants followed the routine national prevention of mother-to-child transmission programmes (PMTCT) until trial inclusion at day 7 after birth. These programmes included zidovudine from 28 weeks of pregnancy until birth, intrapartum single-dose nevirapine, then zidovudine–lamivudine for 7 days after birth for mothers; and 7 days of nevirapine from birth for infants.

Infants were eligible for inclusion at day 7 (ie, end of protection by nevirapine) if they were: singleton; breastfed at day 7 by their mothers; had a negative HIV-1 DNA PCR at day 7; had received any PMTCT; and if the mother was aged 18 years or older, intended to continue breastfeeding, was HIV-1 infected, and was not eligible for ART (either clinically or because CD4 count <350 cells per μL) nor taking ART, had received any perinatal antiretroviral prophylaxis during pregnancy or delivery, resided within the study area, was not intending to move out of the area in the next year, and gave consent to participate for herself and her infant. Infants were not included if they had clinical signs or biological abnormalities of grade 2 or higher on the US National Institutes of Health Division of AIDS (DAIDS) adverse events grading tables, with exceptions for haemoglobin (not included if haemoglobin <120 g/L) and absolute neutrophil count (not included if neutrophils <1200 cells per μL [$1{\cdot}20\times10^9$/L]); or if they presented with serious congenital malformations or birthweight was 2·0 kg or lower.

The study protocol has been approved by the Ethical Committee for Health Research in Burkina Faso, the Biomedical Research Ethics Committee in Zambia, the Uganda National Council for Science and Technology, the Stellenbosch University Ethics committees, the Medicines Control Council in South Africa, and the Regional Committee for Medical Research Ethics of Norway. All participating mothers gave written informed consent.

### Randomisation and masking

We randomly assigned HIV-1-uninfected infants on day 7 (plus or minus 2 days) to either lopinavir–ritonavir or lamivudine in a 1:1 ratio. An independent statistician generated the randomisation lists online using the website randomization.com, with stratification by country and in permuted blocks of four and six. The statistician prepared sequentially numbered envelopes corresponding to the order of codes on the randomisation list. Study pharmacists used these sealed opaque envelopes to assign participants.

We used locally available drugs for both lopinavir–ritonavir and lamivudine groups. All bottles were masked with a study label that prevented primary caregiver or parent from reading the original label. Participants, study

physicians, and statisticians were not aware of treatment allocation, and assessors were fully blind and had no contact with patients. However, given that masking was only partial, some parents might have known their child's treatment allocation.

### Procedures

Infants received paediatric liquid formulations of either lopinavir–ritonavir (Kaletra, Abbott, Chicago, USA); 40 mg of lopinavir and 10 mg of ritonavir, twice a day if weighing 2–4 kg, and 80 mg and 20 mg, twice a day if weighing >4 kg) or generic lamivudine (7·5 mg twice a day if weighing 2–4 kg, 25 mg twice a day if weighing 4–8 kg, and 50 mg twice a day if weighing >8 kg). Drugs were renewed monthly by the study pharmacist who weighed returned bottles to assess adherence. Study pharmacists did randomisation, drug delivery, and adherence counselling, allowing study physicians and clinical staff to remain masked to drug allocation. Drug adherence was defined as the proportion of the drugs consumed as measured by bottle weight over the amount of drug that should have been taken over the same period of time.

Mothers diagnosed with HIV-1 infection during routine antenatal care were invited to attend a screening visit in which eligibility for ART was assessed. After delivery, we did a second screening visit to focus on child eligibility criteria before day 5. Children were enrolled at day 7 (plus and minus 2 days) after birth. Follow-up visits for drug renewal, adherence, and breastfeeding support; clinical examination; adverse events assessment; and collection of infant feeding data were scheduled at 2 weeks after enrolment then every 4 weeks until week 50. Infant HIV-1 infection was assessed using HIV-1 DNA real-time PCR on dried blood spots (Generic HIV DNA cell, Biocentric, France)[18] at day 7 and at weeks 6, 14, 26, 38, and 50 (appendix). HIV-1 infection was confirmed by the same technique on a second sample. Venous blood was also collected from infants at weeks 6, 26, and 38 to check for biological abnormalities.

Maternal HIV-1 status assessment relied on the national diagnostic algorithms based on a combination of rapid tests or ELISAs or both and was confirmed on a second sample during the antenatal screening visit. We measured CD4 cell count by flow cytometry. Finally, we quantitated maternal HIV-1 RNA with a commercial real-time RNA PCR test (Generic HIV Charge Virale, Biocentric, France).[19] All biological assays were carried out at the four sites after technology transfer and establishment of an external quality control scheme.

Mothers, through regular counselling about infant feeding practices, were encouraged to exclusively breastfeed their children for 6 months, to introduce complementary feeds gradually thereafter, and to stop breastfeeding completely no later than 49 weeks. The study drug was stopped either 1 week after complete cessation of breastfeeding or at the final visit at week 50.

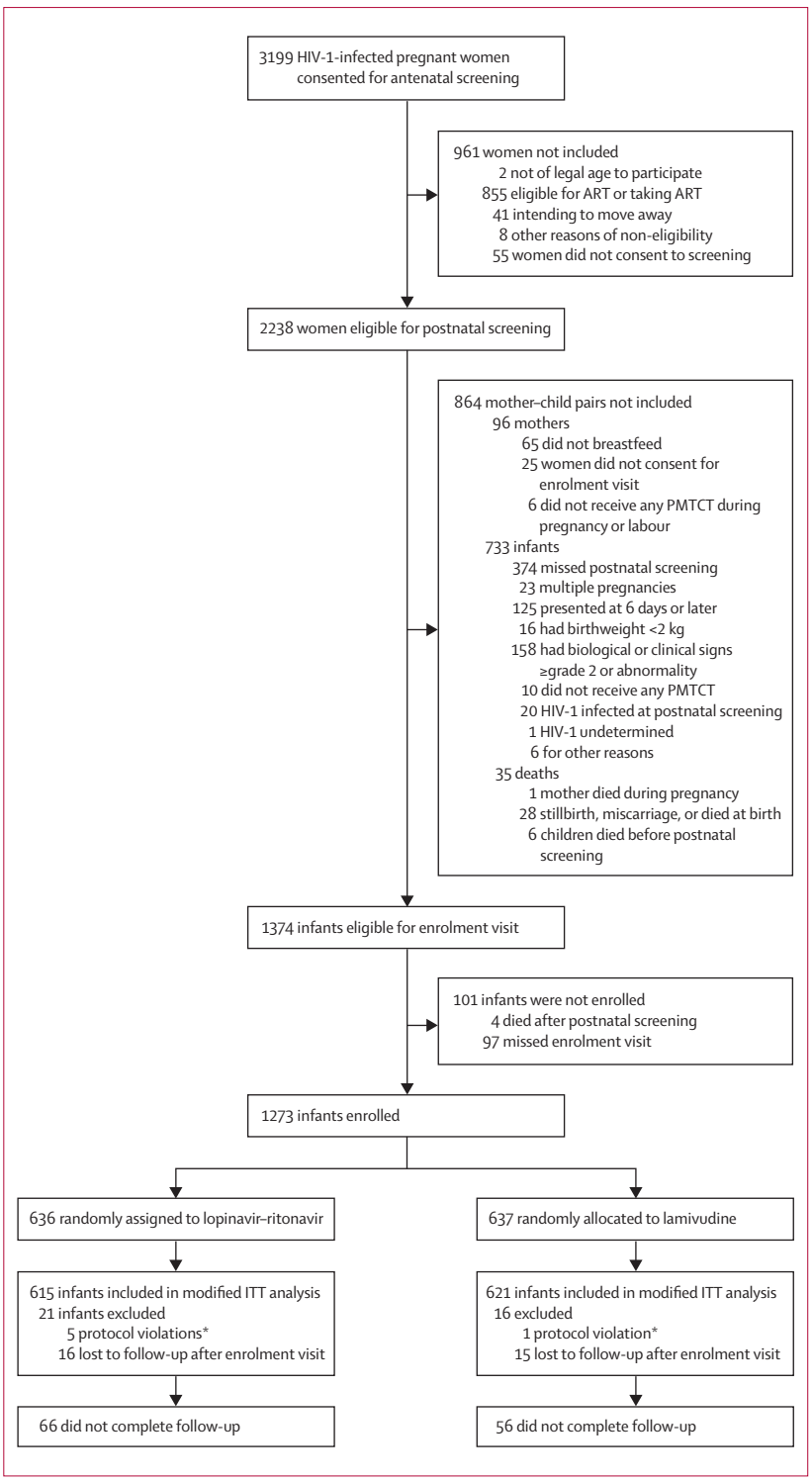


***Figure 1:*** **Trial profile**
ART=antiretroviral therapy. PMTCT=prevention of mother-to-child transmission. ITT=intention to treat. *All protocol violations related to mis-enrolments; five in the lopinavir–ritonavir group (two mothers taking ART, one infant infected by HIV-1 at postnatal screening, one mother did not want to continue breastfeeding up to 6 months, one infant with congenital abnormality) and one in the lamivudine group (one infant infected by HIV-1 at postnatal screening).

| | Lopinavir–ritonavir group (n=631) | Lamivudine group (n=636) |
|---|---|---|
| **Mothers** | | |
| Age (years) | 27·1 (23·8–31·2) | 27·0 (22·9–30·9) |
| Parity | 2·8 (1·5) | 2·7 (1·5) |
| Pre-delivery CD4 count (cells per µL) | 528 (430–667) | 531 (437–673) |
| Plasma HIV-1 RNA | | |
| Undetectable | 275 (44%)* | 276 (45%)† |
| Median ($log_{10}$ copies per mL) | 3·4 (2·9–3·9) | 3·4 (3·0–3·9) |
| WHO clinical HIV-1 staging | | |
| Stage I | 613 (97%) | 612 (96%)‡ |
| Stage II | 17 (3%) | 22 (4%) |
| Stage III–IV | 0 | 1 (<1%) |
| Unknown stage | 1 (<1%) | 0 (0%) |
| PMTCT regimen | | |
| During pregnancy | 608 (96%) | 612 (96%) |
| During labour | 615 (98%) | 626 (98%) |
| Highest education level completed | | |
| None | 80 (13%) | 85 (13%) |
| Primary | 234 (37%) | 219 (34%) |
| Secondary or tertiary | 317 (50%) | 332 (52%) |
| **Infants** | | |
| Boys | 322 (51%) | 335 (53%) |
| Girls | 309 (49%) | 301 (47%) |
| Birthweight (g) | 3000 (2740–3350) | 3000 (2800–3325) |

Data are mean (SD), median (IQR), or n (%). *Nine missing values. †19 missing values. ‡One missing value.

***Table 1:*** **Characteristics of correctly enrolled mothers and infants at enrolment by group**

### Outcomes

The primary outcome was acquisition of HIV-1 in infants between age 7 days and 50 weeks. The prespecified secondary outcomes were HIV-1-free survival from day 7 to 50 weeks (event: infant death or acquisition of HIV-1 infection in infants), severe adverse events (DAIDS adverse event grade 3 or 4) possibly related or with undetermined relation to the study drug (according to ANRS severe adverse events reporting procedures), up to 50 weeks.

### Statistical analyses

Sample size calculation and assumptions used for superiority analysis of the primary outcome have been reported.[17] We used a modified intention-to-treat approach for primary analyses, including all infants correctly enrolled who attended at least one follow-up visit. A secondary per-protocol analysis for HIV-1 infection included all children with a drug adherence higher than 80% during the prophylaxis period, with censoring when they withdrew from study drug or when breastfeeding stopped (whichever came first) or at the time of the last visit before two or more consecutive missed visits.

We estimated the cumulative probability of HIV-1 infection with Turnbull's extension of the Kaplan-Meier procedure to interval-censored data.[20] We estimated 95% CIs by bootstrapping. Since the times to events were known, we estimated secondary outcome probabilities (mortality, and HIV-1 or death) using the Kaplan-Meier procedure and calculated their 95% CIs using a log-log transformation. We supposed that HIV-1 infection occurred at midpoint between the last HIV-1 DNA negative test and the first HIV-1 DNA positive test. Infants who remained HIV-1-uninfected were censored at their last HIV-1 negative test. For HIV-1-free survival analyses, children were censored at the earliest time they met the endpoint (HIV-1-infection or death) or at their last known date with vital status and no HIV-1 infection. We estimated all hazard ratios (HR) using a crude Cox model. We also estimated Kaplan-Meier curves of complete breastfeeding cessation, HIV-1 infection, mortality, and HIV-1-free-survival for each group, and compared them using a log-rank test. When the risk-probability assumption was not met for the latter test, we used a piecewise model[21] to compare survival curves. We used Fisher's exact test to compare severe adverse events between groups. We did statistical analyses with SAS version 9.3 for Windows and R version 2.15.1.

An independent data monitoring committee recommended not to carry out interim analyses on the basis of the lower than expected number of HIV infections at mid-trial. This committee also compared regularly the serious adverse events between arms during the study, and approved the database readiness for statistical analyses. The trial is registered with ClinicalTrials.gov, number NCT00640263.

### Role of the funding source

The sponsor and funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

## Results

Between Nov 16, 2009, and May 7, 2012, we enrolled 1273 HIV-1-exposed infants. Six children were wrongly enrolled (protocol violations) and 31 never returned after enrolment, leaving 1236 infants included in the modified intention-to-treat analysis; 615 randomly assigned to lopinavir–ritonavir and 621 to lamivudine (figure 1). 66 infants assigned to lopinavir–ritonavir and 56 assigned to lamivudine did not complete follow-up, but were included in analysis with date from their last assessment (figure 1). Baseline characteristics of the 1267 correctly enrolled infants and their mothers were similar across groups (table 1), with some differences between countries (appendix). The median age of mothers was 27·1 years (IQR 23·3–31·1), their antenatal median CD4 count was 529 cells per µL (IQR 432·0–669·0), and 551 (45%) had undetectable plasma HIV-1 RNA at day 7. Overall, 1112 (88% of all correctly enrolled) infants attended the final visit with an HIV-1 test and 33 (3%) died during follow-up.

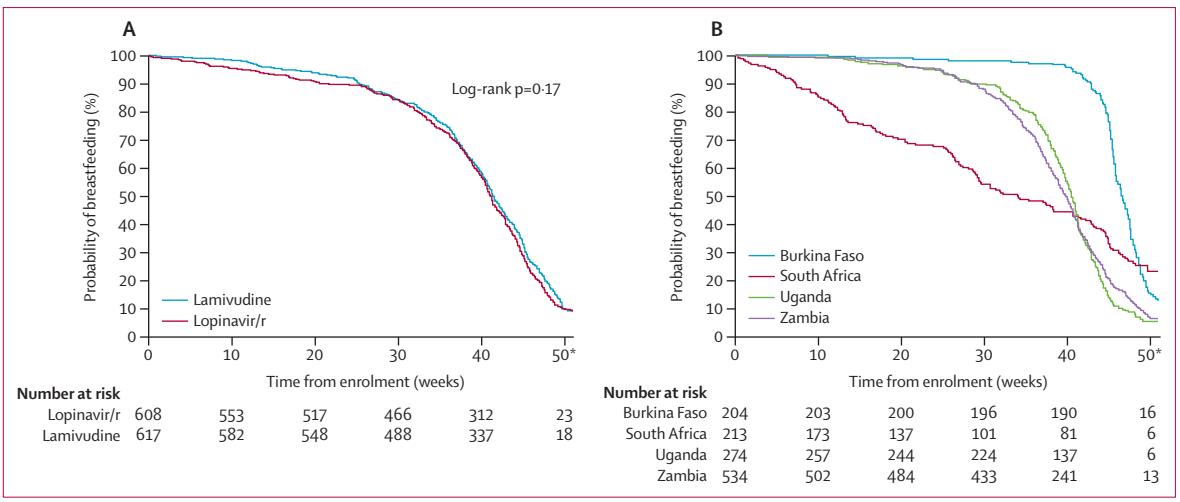


***Figure 2:*** **Breastfeeding cessation by study group (A) and by country (B)**
Lopinavir/r=lopinavir–ritonavir. *Corresponding to final visit: 50 weeks of age (plus or minus 2 weeks).

The mean drug adherence was high and slightly better in the lamivudine group (93% [SD 15%]) than in the lopinavir–ritonavir group (90% [14%]; p<0·0001). On average, infants were on study drug (irrespective of adherence level) 95% (SD 16%) and 94% (18%) of days they were breastfed plus 1 week, in the lopinavir–ritonavir and lamivudine groups, respectively.

The overall median duration of any breastfeeding was 41·1 weeks (IQR 34·4–45·6) in the lopinavir–ritonavir group and 41·4 weeks (35·9–46·7) in in the lamivudine group (figure 2A). Zambia and Uganda had similar curves of breastfeeding over time, Burkina Faso had a more prolonged duration of breastfeeding and conversely, breastfeeding was stopped much earlier in South Africa (Figure 2B). At week 26, the probability of still breastfeeding was 99% in Burkina Faso, 68% in South Africa, 94% in Uganda, and 94% in Zambia. At week 50, the corresponding numbers were 13%, 23%, 5%, and 7%, respectively.

Between day 7 and week 50, 17 infections with HIV-1 were confirmed in infants: eight in those assigned to lopinavir–ritonavir and nine in those assigned to lamivudine, giving a cumulative postnatal transmission rate of 1·4% (95% CI 0·4–2·5) and 1·5% (0·7–2·5), respectively (p=0·83; figure 3A) and an HR for lopinavir–ritonavir versus lamivudine of 0·90 (95% CI 0·35–2·34; p=0·83).

Between day 7 and 26 weeks, four infants in the lopinavir–ritonavir group became infected, giving a transmission rate of 0·6% (95% CI 0–1·4), and five infants in the lamivudine group became infected, giving a transmission rate of 0·8% (0–1·5). In the per-protocol analysis (infants with high adherence), which included 990 infants (474 in the lopinavir–ritonavir group and 516 in the lamivudine group), only one transmission (0·2%; 95% CI 0·0–1·6) occurred in the lopinavir–ritonavir group and four (0·8%; 0·3–2·5) in the lamivudine group up to 50 weeks, with no difference between the two groups (HR 0·28, 95% CI 0·03–2·46, p=0·25).

Pooling the two groups, the cumulative transmission rate was 0·7% (n=9; 95% CI 0·2–1·2) at 26 weeks and 1·5% (n=17; 0·8–2·2) at 50 weeks. Eight of 17 (47%) transmissions occurred after 6 months. At 50 weeks, among the 691 women with antenatal CD4 count of 500 cells per µL or higher, the pooled transmission rate was 0·8% (n=6; 95% CI 0·2–1·5), whereas it was 2·3% (n=11; 1·0–3·6) among the 520 women with antenatal CD4 count 350–500 cells per µL ($p_{interaction}$=0·19; appendix).

Between day 7 and week 50, 33 children died, resulting in an overall mortality rate of 2·8% (95% CI 2·0–3·9). Mortality rates were 3·0% (n=18; 1·9–4·8) in infants assigned to lopinavir–ritonavir and 2·5% (n=15; 1·5–4·1 in those assigned to lamivudine, without difference between groups (HR 1·22, 95% CI 0·61–2·42, p=0·57; figure 3B). However, mortality rates varied across sites (appendix). All infants who died had a negative HIV-1 DNA PCR test when last tested, which was a median of 5 weeks (IQR 3·3–8·7) before death. No death was deemed attributable to the study drugs.

At 50 weeks, the probability for a child to be alive without HIV-1 infection was 96% (n=581; 93·6–97·0) in the lopinavir–ritonavir group and 96% (n=586; 94·0–97·3) in the lamivudine groups, without difference between groups (HR 1·10, 0·63–1·92; p=0·74; figure 3C). This probability was higher in Burkina Faso (n=201; 98·5%, 95% CI 95·5–99·5) and South Africa (n=206; 98·5%, 95·5–99·5), than in Zambia (n=505; 95·1%, 92·8–96·7) and Uganda (n=255; 92·9%, 89·2–95·4).

497 severe adverse events were reported, 251 (51%) in the lopinavir–ritonavir group and 246 (50%) in the lamivudine group (p=0·86). 218 (36%) infants in

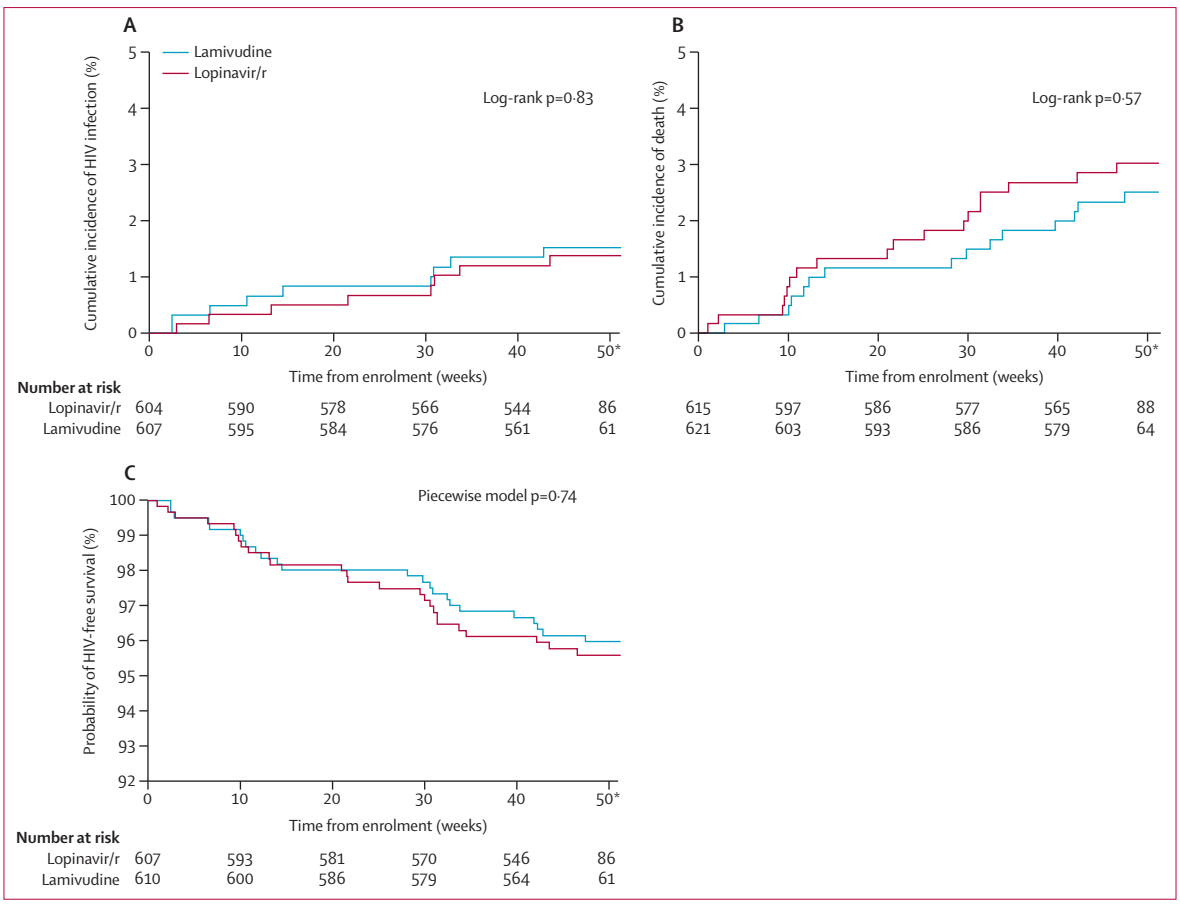


***Figure 3:*** **Kaplan-Meier survival outcomes for HIV-1 infection (A), mortality (B), and HIV-1-free survival (C) by study group**
Lopinavir/r=lopinavir–ritonavir. *Corresponding to final visit: 50 weeks of age (plus or minus 2 weeks).

| | Lopinavir–ritonavir group (n=615) | Lamivudine group (n=621) | p value* |
|---|---|---|---|
| Anaemia | 113 (18%) | 101 (16%) | 0·33 |
| Neutropenia | 68 (11%) | 70 (11%) | 0·93 |
| Malaria | 10 (2%) | 14 (2%) | 0·54 |
| Hyponatraemia | 10 (2%) | 12 (2%) | 0·83 |
| Pneumonia | 13 (2%) | 7 (1%) | 0·18 |
| Diarrhoea | 7 (1%) | 12 (2%) | 0·36 |
| Septicaemia | 5 (1%) | 5 (1%) | 1 |
| Severe malnutrition | 5 (1%) | 4 (1%) | 0·75 |
| Hypertriglyceridaemia | 0 | 1 (<1%) | 1 |
| Hypercholesterolaemia | 6 (1%) | 3 (<1%) | 0·34 |
| Renal failure | 3 (1%) | 4 (1%) | 1 |
| Thrombocytopenia | 2 (<1%) | 4 (1%) | 0·69 |
| Hypokalaemia | 4 (1%) | 1 (<1%) | 0·22 |
| Hypernatraemia | 1 (<1%) | 3 (<1%) | 0·62 |

Grading by US National Institutes of Health, Division of AIDS. *Fisher's exact test for lopinavir–ritonavir versus lamivudine.

***Table 2:*** **Proportion of individuals who had one grade 3 or 4 adverse event**

the lopinavir–ritonavir group and 206 (33%) in the lamivudine group had at least one severe adverse event ($p_{difference}$=0·40). None of the grade 3–4 serious adverse events occurred more frequently in one group than in the other (table 2). The most common severe adverse events were anaemia (n=214; 17%), neutropenia (n=138; 11%), malaria (24; 2%), hyponatraemia (n=22; 2%), and pneumonia (n=20; 2%; table 2).

## Discussion

Our study showed that two infant PreP regimens, using lopinavir–ritonavir or lamivudine, were equally well tolerated and effective to reduce postnatal HIV-1 transmission incidence to lower than 1·5%. The trial is unique in that it assessed a postnatal PMTCT strategy (infant PreP) for the recommended 12 months duration of breastfeeding and that it compared head-to-head two antiretroviral drugs for infant PreP. In our trial, the comparative regimen was lamivudine and not nevirapine because the lamivudine has proven efficacious,[7] is associated with less frequent and less severe side-effects,[3] and if resistance occurs, it does not extend to the whole class of drugs, unlike for nevirapine.

About half of the postnatal HIV-1 infections in both groups occurred after 6 months of breastfeeding, while HIV-1 exposure was much reduced during this period because of mixed feeding (lowering milk intakes) and some breastfeeding cessations before 50 weeks. This finding justifies the extension of infant PreP until the end of HIV-1 exposure and the need to inform mothers about the persistent risk of transmission throughout breastfeeding to prevent adherence fatigue.

WHO recommends stopping infant PreP 1 week after the complete cessation of breastfeeding. In our trial, we followed this recommendation and two infants became infected because breastfeeding was not completely stopped or was resumed. This finding suggests consideration of a longer period of infant PreP after cessation of breastfeeding or that infant prophylaxis should not be stopped until no milk can be expressed during clinical examination from the mother breasts or both.

Comparisons between our findings and those of other studies[3,4,6–12,22] are available in the appendix. Overall, both lamivudine and lopinavir–ritonavir led to very low rates of HIV-1 postnatal transmission in comparison with other studies that used option A or B, at both 6 months and 12 months.

Because antiretroviral prophylaxis is potentially given to large numbers of uninfected infants, safety is important for choosing of the best drug. Our findings were reassuring because both drugs were well tolerated with no additional severe adverse events in those assigned to lopinavir–ritonavir than in those given lamivudine, for which safety is already documented in neonates. In 2012, the US Food and Drug Administration raised concerns about the use of lopinavir–ritonavir in preterm or underweight babies,[23] which came after a French report of transient adrenal dysfunction in newborn infants exposed in-utero to lopinavir–ritonavir.[24] In our trial, which excluded neonates who weighed less than 2·0 kg as a proxy of prematurity, no infant died with signs of adrenal dysfunction. Biological monitoring of hyponatraemia, hyperkalaemia, and renal function did not record more frequent disturbances in the lopinavir–ritonavir group. However, longer-term safety monitoring is needed.

Adherence to the regimens was excellent in the two groups and much higher than the adherence reported for maternal ART by several studies.[25] Although not quantifiable, maintenance of good adherence in the lopinavir–ritonavir group needed additional efforts because of its poor palatability. Despite good adherence overall, the much lower number of infections in the per-protocol population analysis strongly suggests that most infections resulted from poor drug adherence. Drug adherence therefore remains a key factor for success of infant PreP. More research is needed for more palatable oral paediatric formulations and longacting injectable drugs.

Our trial had some limitations. The lower than expected number of infections resulted in a low power to detect a difference in the main outcomes between groups. Although we could not rule out that some HIV-1 transmissions were missed among children who did not complete the study, infants who discontinued early (mainly due to moving home or early breastfeeding cessation) were probably not at higher risk for HIV-1. Although possible, deaths were probably not due to undiagnosed HIV-1 infection given the narrow period since the last HIV-1-negative test.

Our cohort includes four countries from various African regions, which had different infant feeding practices and different circulating HIV-1 subtypes, making our findings relevant to all sub-Saharan Africa. WHO's consolidated guidelines[26] from June, 2013, recommend the initiation of lifelong maternal ART during pregnancy regardless of CD4 count, based mostly on presumed practicalities and mathematical modelling, not on evidence-based arguments.[27] This strategy has proven highly efficacious for preventing perinatal transmission, but may be insufficient to avoid HIV-1 transmission by breastfeeding (appendix). Unsatisfactory drug adherence in routine practice[25] and absence of ART effect on cell-associated virus in breastmilk[28] are proposed as the main potential limiting factors. In addition, implementation of the B+ option is facing many difficulties in the field.[29] Accumulating programmatic evidence from a meta-analysis showed that maternal ART adherence at 1 year after initiation during pregnancy was only 53%,[25] leaving a huge number of breastfed babies unprotected. Also, maternal viral rebound after ART withdrawal might increase the risk of transmission to breastfed children. Adherence to infant PreP is also key. However, adherence to infant PreP is likely to be driven by very different determinants than is adherence to maternal ART. The excellent drug adherence and effectiveness against mother-to-child HIV transmission we report, particularly in babies of women with more than 500 CD4 cells per µL (the main target of the option B+ strategy), is very reassuring in this respect.

Infant PreP proved an effective and safe alternative to prevent postnatal HIV-1 transmission for mothers who are not ready or prepared to embark on long-term ART. In addition, adding infant PreP in breastfed babies whose mothers are taking ART is a strategy that should be assessed. The additional toxicity is probably small since very low quantities of antiretroviral drugs taken by the lactating mother are present in breastmilk.[30] In the HPTN046 study,[4] no additional toxicity was reported among infants randomly assigned to nevirapine versus placebo whose mothers were taking ART. At the population level, in countries where universal maternal ART cannot be implemented as recommended by WHO, infant PreP with either lopinavir–ritonavir, lamivudine, or nevirapine for the whole duration of breastfeeding is also advisable.

**Contributors**

NN, TT, and PVdP designed the trial. TT, NN, DNev, CL, HS, CK, IMSE, NM, JKT, GJH, and PVdP wrote the final version of the protocol. CK, NM, JKT, GN, DJ, ES, DR, and GJH coordinated the field and laboratory work in the four African study sites. DNeb, HT, MK, AS, and MS collected the data and conducted enrolment and follow-up of participants. NN and RV proceeded to the data management and NN, RV, and MP analysed the data. NN, TT and PVdP wrote the first draft of the manuscript. PVdP coordinated the revised versions and is responsible for final content. All authors reviewed and approved the final version of the manuscript.

**Declaration of interests**

We declare no competing interests.

**Acknowledgments**

The French National Institute of Health and Medical Research–National Agency for Research on AIDS and Viral Hepatitis (Inserm–ANRS) sponsored the study. Funding was provided by Inserm-ANRS (ANRS 12174) including funds from the Total Foundation, European Developing Countries Clinical Trials Partnership (EDCTP; grant number CT.2006.33020.004) and the Research Council of Norway (GlobVac grant number 183600). We thank the French Agency for AIDS Research (ANRS) and particularly Brigitte Bazin and Jean-François Delfraissy (Director) for their constant encouragement and support. Our gratitude extends to the EDCTP and particularly Charles Mgone (Director) and Montserrat Blazquez as well as to the Global Health and Vaccination Research Program (GLOBVAC) at the Research Council of Norway. We thank the independent data monitoring committee (Simon Cousens [London School of Hygiene & Tropical Medicine, UK], Sithembiso Velaphi [Witwatersrand University, South Africa], Laurent Mandelbrot [Paris 7 University, France], Isabelle de Vincenzi [WHO, Geneva], and Gunnel Biberfeld [Karolinska Institute, Sweden]) and our scientific advisory board (Nigel Rollins [WHO], Rodolphe Thiebaut [University of Bordeaux, France], and Kusum Nathoo [University of Zimbabwe, Harare, Zimbabwe]) for their commitment and their invaluable support for the ANRS 12174 trial. We thank Audrey Jaussent for the elaboration of the randomisation lists. We thank all the women and their infants who agreed to participate in the trial.

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