Twenty-four month efficacy of a maternal short-course zidovudine regimen to prevent mother-to-child transmission of HIV-1 in West Africa

Valériane Leroy[a], John M. Karon[b], Ahmadou Alioum[a], Ehounou R. Ekpini[c], Nicolas Meda[d], Alan E. Greenberg[b], Philippe Msellati[e,f], Michael Hudgens[g], François Dabis[a] and Stefan Z. Wiktor[b], for the West Africa PMTCT Study Group*

Objective: To assess the 24 month efficacy of a maternal short-course zidovudine regimen to prevent mother-to-child transmission (MTCT) of HIV-1 in a breastfeeding population in West Africa.

Methods: Data were pooled from two clinical trials: DITRAME-ANRS049a conducted in Abidjan, Côte d'Ivoire and Bobo-Dioulasso, Burkina-Faso and RETRO-CI, conducted in Abidjan. Between September 1995 and February 1998, consenting HIV-1-seropositive women were randomly assigned to receive zidovudine (300 mg) or placebo: one tablet twice daily from 36–38 weeks' gestation until delivery, then in DITRAME only, for 7 more days. Paediatric HIV-1 infection was defined as a positive HIV-1 polymerase chain reaction, or if aged $\geq$ 15 months, a positive HIV-1 serology. Cumulative risks (CR) of infection were estimated using a competing risk approach with weaning as a competing event.

Results: Among 662 live-born children, 641 had at least one HIV-1 test. All but 12 children were breastfed. At 24 months, overall CR of MTCT were 0.225 in the zidovudine and 0.302 in the placebo group, a 26% significant reduction. Among children born to women with CD4 cell counts $<$ 500/ml at enrolment, CR of MTCT were similar, 0.396 in the zidovudine and 0.413 in the placebo group. Among children born to women with CD4 cell counts $\geq$ 500/ml, CR of MTCT were 0.091 in the zidovudine and 0.220 in the placebo group, a significant 59% reduction.

Conclusion: A maternal short-course zidovudine regimen reduces MTCT of HIV-1 at age 24 months, despite prolonged breastfeeding. However, efficacy was observed only among women with CD4 cell counts $\geq$ 500/ml. New interventions should be considered to prevent MTCT, especially for African women with advanced HIV-1 immunodeficiency.

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From the [a]Unité INSERM 330, Université Victor Segalen Bordeaux 2, Bordeaux, France; [b]Centers for Disease Control and Prevention, Atlanta, GA, USA; [c]Projet RETRO-CI, Abidjan, Côte d'Ivoire; [d]Centre Muraz, OCCGE, Bobo-Dioulasso, Burkina Faso; [e]IRD UR 091, Marseille, France; [f]PAC-CI Programme, Abidjan, Côte d'Ivoire; and [g]Fred Hutchinson Cancer Research Center, Seattle, WA, USA.

*See Appendix for members of the West Africa PMTCT Study Group.

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Correspondence to: Valeriane Leroy, MD, PhD, Unité INSERM 330, Université Victor Segalen Bordeaux 2, 146, rue Léo Saignat, 33076 Bordeaux Cedex, France.

Tel: +33 5 57 57 12 58; fax: +33 5 57 57 45 28; e-mail: valeriane.leroy@isped.u-bordeaux2.fr

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Introduction

In Africa, the postnatal transmission (PT) of HIV-1 through breastfeeding is of great concern. Recently, the results of a randomized trial comparing breastfeeding with formula feeding in the absence of any other intervention [1] showed that the excess risk of mother-to-child transmission (MTCT) of HIV-1 attributable to breastfeeding is substantial, an absolute risk of 16% at 2 years, with 44% of all MTCT attributable to PT. PT could substantially reduce the overall long-term effect of peripartum antiretroviral interventions to prevent MTCT [2,3]. Pilot public health programmes to reduce MTCT around the time of birth are starting in African breastfeeding populations [4], and international guidelines encouraging them have been made available by the World Health Organization [5]. Because of the risk of infection through breastfeeding, the long-term efficacy of these interventions must be assessed.

In February 1998, a randomized clinical trial [6] showed that a maternal short-course regimen of oral zidovudine reduced by half the MTCT of HIV-1 to non-breastfed children in Thailand. As a result, two similar randomized trials conducted in African breastfeeding populations stopped enrolment in February 1998. These African trials also demonstrated a reduction of early MTCT, 37% at 3 months of age [7] and 38% at 6 months [8]. Preliminary information from the trials suggested that the efficacy of zidovudine is maintained at 15 months of age despite prolonged breastfeeding [9,10]. However, individually the trials lacked statistical power to draw conclusions about the impact of PT on the long-term efficacy of maternal short-course zidovudine regimens after the complete cessation of breastfeeding, or the potential effect of other risk factors (such as CD4 cell count) on transmission.

We therefore assessed the 24 month efficacy of a maternal short peripartum regimen of oral zidovudine in reducing the overall risk of MTCT in breastfeeding populations, and evaluated the risk factors for MTCT. This work was a collaboration between the DITRAME (French National AIDS Research Agency, ANRS) and Projet RETRO-CI (Côte d'Ivoire Ministry of Health and US Centers for Disease Control and Prevention) teams.

Methods

We pooled individual data from two randomized double-blind placebo-controlled trials: DITRAME ANRS-049a conducted in Abidjan, Côte d'Ivoire and Bobo-Dioulasso, Burkina-Faso [8] and RETRO-CI conducted in Abidjan [7]. The trial protocols were approved by the ANRS and Centers for Disease Control and Prevention ethical review boards, respectively, and by the Ethical Committee of the Côte d'Ivoire National Ministries of Health. Between September 1995 and February 1998, consenting eligible pregnant HIV-1-seropositive women with haemoglobin levels of 70 g/l or greater were randomly assigned at 36–38 weeks' gestation to receive oral zidovudine (250 or 300 mg) or a matching placebo (Table 1): one tablet twice a day until the beginning of labour; then in DITRAME, a single oral dose of 500 or 600 mg, and in RETRO-CI, one 300 mg tablet every 3 h until delivery; then (in DITRAME only) a 7 day postpartum maternal treatment of 500 or 600 mg per day. No treatment was given to the neonate.

Maternal lymphocyte sub-types at entry were counted by standard flow cytometry (FACScan, Becton Dickinson, Dartford, UK). Clinical follow-up of and blood collection from each live-born child were scheduled within one week after birth, then at 4 weeks (RETRO-CI) or 6 weeks (DITRAME), then at 3 months of age and every 3 months thereafter until 24

Table 1. Description of oral zidovudine regimens and sample size in the two randomized clinical trials included in the pooled analysis: DITRAME ANRS-049[a] and RETRO-CI trials, Abidjan and Bobo Dioulasso, 1995–1998.

Name of trial (Trial promoter)	Prepartum treatment[a]	Intrapartum treatment	Maternal postpartum treatment	Children postnatal treatment	Number of women enrolled	Number of children included in the analysis[b]
DITRAME ANRS-049a (ANRS)	Phase 2: 500 mg bid Phase 3: 600 mg bid	Single dose Phase 2: 500 mg Phase 3: 600 mg	7 Days Phase 2: 500 mg bid Phase 3: 600 mg bid	None	421 (212 in placebo group)	391
RETRO-CI (US Centers for Disease Control)	All: 600 mg bid	300 mg every 3 h	None	None	280 (140 in placebo group)	250

bid, Twice a day.
[a]From 36 to 38 weeks' gestational age.
[b]All live-born children, excluding the second twin born of each twin pair and those indeterminate for HIV status (no test available).

months of age. Infant feeding practices were reported at each visit on standardized questionnaires.

For each child, the sample collected at 3 months (RETRO-CI) or 6 months (DITRAME), or an earlier sample when these were not available, was analysed by polymerase chain reaction (PCR). If this sample was positive, all the preceding available samples were analysed by PCR. PCR was used for samples obtained until 9 months of age for DITRAME and 12 months for RETRO-CI. HIV-1-DNA nested PCR was used in Abidjan, with primers from the protease gene (DITRAME and RETRO-CI). In Bobo Dioulasso (DITRAME), samples were analysed during phase 2 by both DNA PCR and quantitative plasma RNA PCR (Amplicor HIV Monitor version 1.5, Roche Diagnostic Systems, Inc., Branchburg, NJ, USA) and in phase 3 by RNA PCR only. Serum samples collected between 9 (DITRAME) or 12 months (RETRO-CI) and 24 months of age were screened for HIV-1 and HIV-2 antibodies using a commercial enzyme-linked immunosorbent assay (ELISA, Genelavia Mixt, Diagnostics Pasteur, France; or Murex ICE 1-O-2, Murex Biotech Ltd., UK). Confirmation on the same sample was obtained using a commercial synthetic peptide ELISA (Peptilav 1-2, Diagnostics Pasteur).

Paediatric HIV-1 infection was defined by one positive HIV-1 DNA or RNA PCR test result, or if aged 15 months or over, at least two positive HIV-1 serological tests. A negative diagnosis 60 days or more after the complete cessation of breastfeeding defined the definitive absence of infection. All children with a negative diagnosis on the last available sample obtained while the child was still being breastfed or had been breastfed within the past 59 days were classified as provisionally uninfected. Those children who were stillborn or who had no HIV-1 determination were excluded from the analysis of transmission rates. For all analyses, only the first-born child was used if a woman had had a multiple birth.

Differences between treatment groups in mothers' and babies' characteristics at entry and during follow-up were analysed using Student's *t*-test or the Mann–Whitney test for continuous variables and the Pearson chi-squared test or Fisher's exact test (as appropriate) for categorical variables. The proportions breastfed were estimated using the Kaplan–Meier method and were compared between treatment groups and study sites using the log rank test. To estimate the efficacy of the maternal zidovudine regimen on the overall MTCT risk at 24 months of age, all children with at least one HIV-1 determination were included in a survival analysis comparing groups in an intent-to-treat approach. For infected children, the age when the child would first test positive was interval-censored, with the endpoints of the interval defined as the ages at the last negative test (birth, if no negative test) and the first positive test. The probability of MTCT was estimated non-parametrically using a modification of Turnbull's method for interval-censored data [11] to handle competing risks [12], in which the competing events are a complete cessation of breastfeeding and the acquisition of infection. Definitively uninfected children were regarded as no longer at risk of HIV infection 60 days after the complete cessation of breastfeeding, or right-censored at age 24 months, whichever was earlier. Provisionally uninfected children were right-censored at the age of their last negative test.

For each treatment group, cumulative probabilities of MTCT were estimated for each study site (unless otherwise specified). Standard errors were estimated from a bootstrap with 1000 replications. For each treatment group, the cumulative transmission probability was estimated as the weighted average of the site-specific estimates, with inverse variance weights. As a result, the estimated cumulative risk can decrease with increasing age. Because risk differences between the treatment groups were estimated similarly, some point estimates of these differences are not equal to the differences between the estimated transmission rates. Efficacy was defined as 1 minus the ratio of the probability of transmission in the zidovudine group divided by the corresponding probability for the placebo group. The confidence interval (CI) for an estimate of efficacy was computed using the delta method [13] by estimating the variance of the logarithm of this ratio from variance estimates of the probability of transmission for each treatment group. Probabilities of the combined endpoint of HIV-1 infection or death at selected ages until 24 months were estimated using interval-censored survival analysis methods [14].

The test for a significant difference in the treatment effect in children born to mothers with high versus low CD4 cell counts at enrolment was based on a proportional hazards model and a likelihood ratio test. The proportional hazards assumption was verified using the cox.zph function in S-Plus 2000 (Insightful Inc., Seattle, WA, USA). All other statistical computations were performed in SAS version 8 (SAS Inc., Cary, NC, USA). All statements about statistical significance are based on tests with a type I error of 0.05.

Results

From September 1995 to February 1998, 701 women were enrolled, 421 in DITRAME and 280 in RETRO-CI, of whom 23 (3.3%) were lost to follow-up before delivery (Fig. 1). The 678 women who delivered (408 in DITRAME and 270 in RETRO-CI)

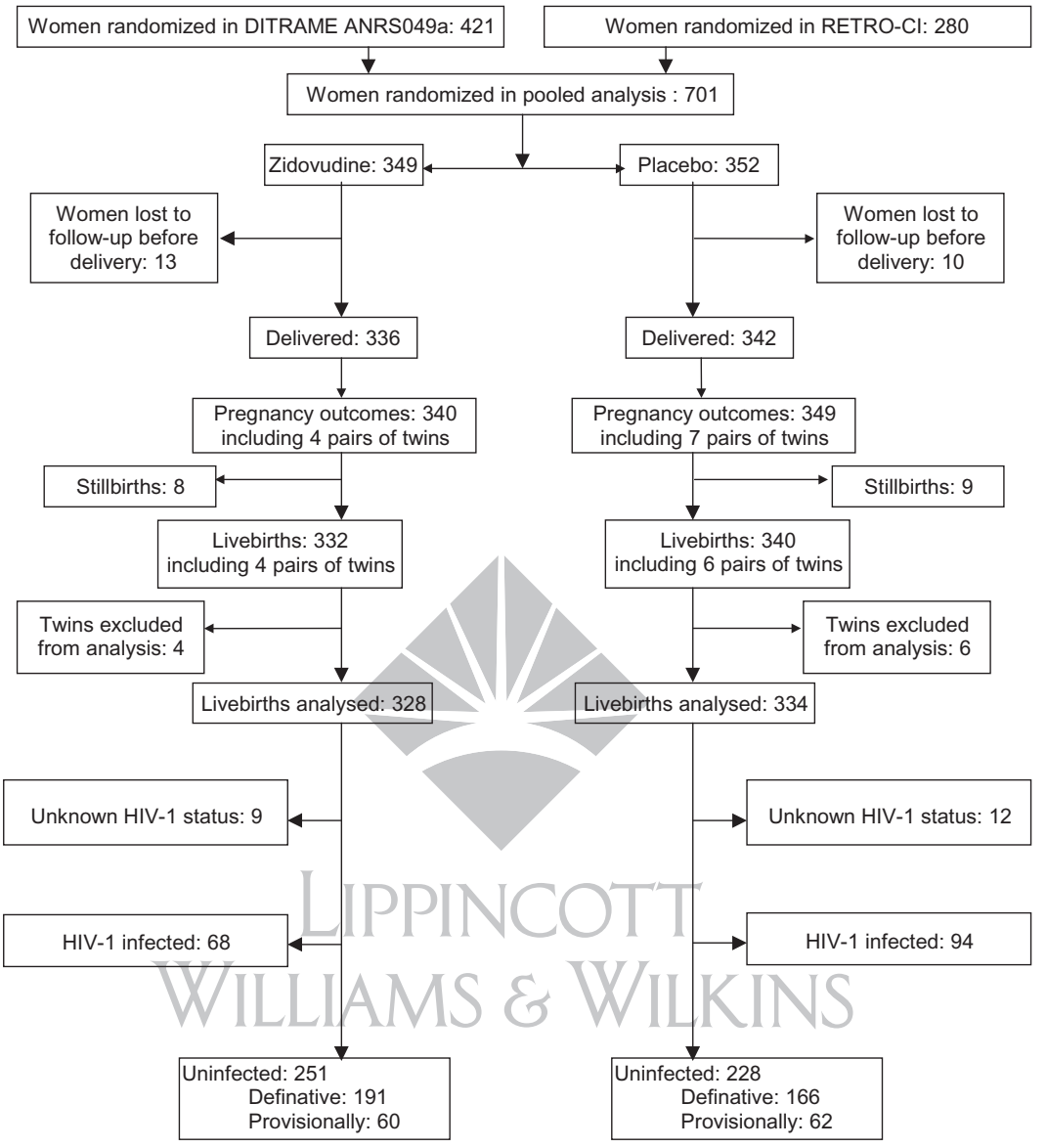

Fig. 1. Pooled trial profile and denominators for analysis of 24 month efficacy (n = 641): DITRAME ANRS-049a and RETRO-CI trials, Abidjan and Bobo Dioulasso, 1995–2000.

had 672 live births and 17 stillbirths (eight in the zidovudine group and nine in the placebo group), including 11 pairs of twins (Fig. 1).

The characteristics of the 678 women who delivered and their use of assigned treatment were similar between the two treatment groups (Table 2). In particular, the median duration of prepartum treatment (23 or 25 days), the proportion receiving intrapartum treatment (81%), and the median length of postpartum maternal treatment (7 days, DITRAME only) were similar. Caesarean section was performed in 2% of women overall.

After exclusion of the second twin, there were 662 live-born children: 328 in the zidovudine arm and 334 in the placebo arm. Among those, 21 (3.2%) children had unknown HIV-1 infection status, nine in the zidovudine group and 12 in the placebo group ($P = 0.55$). Among these 21 children, five of the nine in the zidovudine group and 11 of the 12 in the placebo group died in the neonatal period ($P = 0.06$).

Among the 641 children included in the overall efficacy analysis, 12 were bottle-fed from birth, eight in the zidovudine group and four in the placebo group ($P = 0.23$, Table 3). The age at weaning was not available for one weaned child. Among the remaining 628 children, the probability distributions of breastfeeding duration were similar for the two groups at each site ($P \geq 0.33$) but varied significantly among sites ($P < 0.0001$). The median durations of breastfeeding

Table 2. Characteristics of the 678 mothers who delivered according to the treatment group. DITRAME ANRS-049a and RETRO-CI trials, Abidjan and Bobo Dioulasso, 1995–1998.

Characteristics of women who delivered	Zidovudine n = 336	Placebo n = 342	*P*
Trial/site			
RETRO-CI – Abidjan (%)	135 (39.5)	135 (40.2)	0.97
DITRAME (%)	201 (60.5)	207 (59.8)	
Abidjan	119	121	
Bobo-Dioulasso	82	86	
Median age at entry (IQR) (years)	25 (22–29)	25 (22–30)	0.68[b]
WHO clinical stage at entry (%), DITRAME only			0.48
Stage 1	154 (76.6)	151 (72.9)	
Stage 2	30 (14.9)	31 (15.0)	
Stages 3 or 4[a]	17 (8.5)	25 (12.1)	
CD4 cell count at entry (cells/μl)			
Median (IQR)	545 (355–732)	535 (356–733)	0.87[b]
Missing (%)	5 (1)	8 (2)	
< 200 (%)	24 (7)	27 (8)	
200–349 (%)	54 (16)	51 (15)	
350–499 (%)	70 (21)	67 (20)	
⩾ 500 (%)	183 (54)	189 (55)	
Caesarean section	8 (2.4)	6 (1.8)	0.57
Median (IQR) days of prenatal treatment	23 (14–34)	25 (15–33)	0.68[b]
At least 15 days of prenatal treatment (%)	249 (74.1)	258 (75.4)	0.69
Median % of prenatal doses taken (IQR)	95 (80–100)	97 (80–100)	0.92[b]
At least 80% of prenatal treatment taken (%)	314 (93)	309 (90)	0.42
At least one dose intrapartum (%)	273 (81.3)	278 (81.3)	0.41
Any postpartum dose (%), DITRAME only	189/200 (94.5)	188/200 (94.0)	0.82

IQR, interquartile range.
[a]One stage 4 in each group.
[b]Mann–Whitney test.

were 8.0 months in Abidjan DITRAME [interquartile range (IQR) 6–10], 15.0 months in Abidjan RETRO-CI (IQR 13–17), and 19.4 months in Bobo-Dioulasso (IQR 18–22).

Among the 641 children, median laboratory follow-up was 18 months in both arms (Table 3). By 24 months of age, 68 children born to 319 women assigned to zidovudine and 94 born to 322 women assigned to placebo were known to be HIV-1 infected (Fig. 1, Table 3). Overall, the estimated cumulative risks of HIV-1 infection in the zidovudine group were 12.9% at age 2 weeks, 16.9% at 6 months and 22.5% at 24 months. The corresponding risks in the placebo group were 19.0, 26.1 and 30.2%. At 24 months, the overall risk of MTCT was 7.8% lower in the zidovudine than in the placebo arm (95% CI for the risk difference 0.7–14.9%), a significant 26% reduction in the risk of MTCT (95% CI 2–44%) (Table 4).

The efficacy of zidovudine was greater in children born to women with higher CD4 cell counts at enrolment (Table 5). Among children born to women with CD4 cell counts of less than 500 cells/ml at enrolment, the estimated cumulative risk of HIV-1 infection at age 24 months in the zidovudine group of 39.6% was nearly equal to the corresponding 41.3% risk in the placebo group. This 4% reduction in risk (95% CI −30 to 29%) was not statistically significant. In contrast, among children born to women with CD4 cell counts of 500 cells/ml or greater, the estimated cumulative risks of HIV-1 infection in the zidovudine group were 6.0% at age 2 weeks, 8.8% at 6 months and 9.1% at 24 months. The corresponding risks in the placebo group were 14.7, 19.2 and 22.0%. Among these children, the risk difference between treatment arms at 24 months was 12.7%, with zidovudine efficacy estimated as 59% in reducing the overall MTCT risk (95% CI 28–76%). The formal test for an interaction between maternal CD4 cell count and treatment was marginally significant ($P = 0.07$).

Transmission risks were substantially lower among mothers with CD4 cell counts of 350–499 cells/ml than among those with CD4 cell counts less than 350 cells/ml, but efficacy estimates at age 24 months were similar. Among children born to mothers with CD4 cell counts less than 350 cells/ml, cumulative risks at age 24 months were estimated to be 51.6% in the zidovudine group and 64.2% in the placebo group, a 20% reduction in risk associated with zidovudine use (95% CI −6–39%). Among children born to mothers with CD4 cell counts of 350–499 cells/ml, the corresponding cumulative risks were 22.8 and 26.9%, a 15% reduction in risk associated with zidovudine use (95% CI −59 to 55%).

Table 3. Birth and 24 month follow-up characteristics of the 641 live-born children included in the overall pooled efficacy analysis according to the treatment group. DITRAME ANRS-049a and RETRO-CI trials, Abidjan and Bobo Dioulasso, 1995–2000.

Characteristics	Zidovudine n = 319	Placebo n = 322	*P*
Birth characteristics			
Median (IQR) birth weight (g)	2955 (2700–3195)	2900 (2640–3150)	0.07
Median (IQR) gestational age (weeks) (Ballard or Finnström score)	40 (38.5–40.5)	40 (38.5–40.5)	0.89
Breastfeeding characteristics			
Number of children never breastfed (%)	8 (2.5)	4 (1.2)	0.23
Median (IQR) duration of breastfeeding (ever) (months)	14 (7.8–18)	13 (8.5–18.2)	0.73
Number of children still breastfed at their last follow-up (%)	79 (24.8)	94 (29.6)	0.18
HIV infection status (see definition in Methods)			
Median (IQR) duration of laboratory follow-up (months)	18.3 (12–24)	18.1 (9–24)	0.10
Number of children HIV-1 infected (%)	68 (21.3)	94 (29.2)	0.02
Born to mothers with CD4 cell count < 350/ml at entry (%)	36/74 (48.6)	37/71 (52.1)	
Born to mothers with CD4 cell count 350–499/ml at entry (%)	14/63 (22.2)	18/65 (27.7)	
Born to mothers with CD4 cell count ⩾ 500/ml at entry (%)	16/177 (9.0)	38/179 (21.2)	
Born to mothers with CD4 cell count unknown at entry (%)	2/5 (40.0)	1/7 (14.3)	
Number of children definitively not HIV-1 infected[a] (%)	191 (59.9)	166 (51.6)	0.03
Number of children provisionally not HIV-1 infected at last follow-up (%)	60 (18.8)	62 (19.3)	0.89
Mortality			
Number of live-born children who died (%)	39 (12.2)	68 (21.1)	0.003
Before day 8 (%)	2 (5.1)	2 (2.9)	
Days 8–27 (%)	0 (0.0)	2 (2.9)	
Days 28–365 (%)	26 (66.7)	45 (66.2)	
12–24 months (%)	11 (28.2)	19 (28.0)	

IQR, Interquartile range.
[a]With a negative serological result at least 2 months after complete cessation of breastfeeding.

Efficacy was similar in the two trials: estimated efficacy at ages 6 weeks and 24 months was 36 and 28% in DITRAME (respectively) compared with 48 and 23% in RETRO-CI. Estimated efficacy at age 24 months was similar for women with less than 14 days of prenatal treatment (34%) and women treated for at least 14 days (26%).

Among the 479 children classified as uninfected at age 24 months, the median age at the last negative test was 18 months (IQR 15–25 months). Of these children, 25% (122) were still being breastfed or had stopped breastfeeding for less than 2 months at their last date known uninfected (and thus were still potentially at risk of PT), and 75% were definitive cases of absence of infection (191/251 in the zidovudine group and 166/228 in the placebo group, $P = 0.41$).

At age 24 months, among the children in the transmission analysis, 68 in the placebo group had died (Table

Table 4. Estimated cumulative transmission risk of HIV-1 infection diagnosis at age 24 months in 641 live-born children with an HIV test, DITRAME ANRS-049a and RETRO-CI trials, Abidjan and Bobo-Dioulasso, 1995–2000.

	Children at risk of a first positive test		Cumulative number known infected		Cumulative transmission risk (%) (95% CI)		
Age	Zidovudine	Placebo	Zidovudine	Placebo	Zidovudine	Placebo	Efficacy (%)[a] (95% CI)
2 weeks	319	322	12	18	12.9 (8.9–17.0)	19.0 (13.0–24.9)	32 (−6–56)
6 weeks	301	299	43	68	14.7 (10.6–18.8)	24.8 (19.9–29.6)	41 (17–58)
3 months	262	237	50	78	16.8 (12.5–21.1)	26.1 (21.3–31.0)	36 (12–53)
6 months	241	212	52	82	16.9 (12.6–21.3)	26.1 (21.2–31.0)	35 (11–53)
12 months	227	200	59	88	21.8 (16.6–27.0)	28.1 (23.1–33.1)	22 (−5–42)
18 months	145	127	67	94	22.5 (17.6–27.3)	30.2 (25.0–35.4)	26 (2–44)
24 months	64	56	68	94	22.5 (17.6–27.3)	30.2 (25.0–35.4)	26 (2–44)[b]

CI, Confidence interval.
[a]1 minus the ratio of the estimated transmission risks in the two groups.
[b]Risk difference at 24 months 7.8% (95% CI 0.7–14.9%).
Children no longer at risk of a first positive HIV test include children who completely ceased to be breastfed for at least 60 days or who were lost to follow–up.

Table 5. Estimated cumulative transmission risk of HIV-1 infection diagnosis during the first 24 months of life. Competing risks interval-censored analysis in 629 live-born children whose mothers had a CD4 cell count at enrolment. DITRAME ANRS-049a and RETRO-CI trials, Abidjan and Bobo-Dioulasso, 1995–2000.

Age	CTR (%) of diagnosis of infection (95% CI)		Risk difference placebo–ZDV (95% CI)	Efficacy (%)[a] (95% CI)
	Zidovudine	Placebo		
Maternal CD4 cell count < 500/ml	I/n = 50/137	I/n = 55/136		
2 weeks	20.1 (12.3–27.9)	26.1 (18.0–34.1)	6.0 (−5.8–17.8)	23 (−27–53)
6 weeks	25.6 (17.9–33.3)	32.0 (24.0–40.0)	6.9 (−4.2–18.0)	20 (−18–46)
3 months	27.5 (19.5–35.4)	34.3 (26.1–42.4)	7.4 (−4.2–19.0)	20 (−17–45)
6 months	29.3 (21.4–37.2)	35.3 (27.0–43.6)	6.1 (−5.6–17.8)	17 (−19–42)
12 months	38.5 (29.7–47.3)	38.0 (29.7–46.3)	−0.5 (−13.6–12.5)	−1 (−39–26)
24 months	39.6 (30.8–48.4)	41.3 (32.8–49.8)	2.4 (−9.9–14.8)	4 (−30–29)
Maternal CD4 cell count ⩾ 500/ml	I/n = 16/177	I/n = 38/179		
2 weeks	6.0 (2.3–9.8)	14.7 (8.2–21.2)	7.5 (0.3–15.3)	59 (12–81)
6 weeks	7.7 (3.6–11.8)	19.3 (13.5–25.0)	11.2 (4.0–18.5)	60 (27–78)
3 months	8.4 (4.2–12.5)	19.3 (13.5–25.1)	10.6 (3.5–17.9)	57 (23–76)
6 months	8.8 (4.5–13.1)	19.2 (13.3–25.0)	10.3 (3.0–17.5)	54 (18–74)
12 months	9.1 (4.8–13.4)	20.9 (14.9–27.0)	11.6 (4.1–19.2)	56 (24–75)
24 months	9.1 (4.7–13.5)	22.0 (15.9–28.2)	12.7 (5.1–20.3)	59 (28–76)

CI, Confidence interval; CTR, cumulative transmission risk; I/n, number of children infected/number of children at risk of mother-to-child transmission (MTCT); ZDV, zidovudine.
[a]1 minus the ratio of estimated transmission risks in the two groups. Maternal CD4 cell count at entry was unavailable for the mothers of 12 children: two out of five in the zidovudine group and one out of seven in the placebo group became infected by 24 months.

3), including 53 known to be infected. In the zidovudine group, 39 had died, including 31 known to be infected. In addition, 11 children in the placebo group and five in the zidovudine group had died without any HIV test result.

The efficacy of zidovudine in preventing HIV-1 infection or death was similar to the efficacy in preventing HIV infection alone. Including all live-born children with no HIV test result, by 24 months of age 82 children born to 328 women assigned to zidovudine and 120 born to 334 women assigned to placebo were known to be HIV-1 infected or dead. The maternal CD4 cell count at entry was unavailable for the mothers of 13 children: Two out of eight children in the placebo group and two out of five in the zidovudine group were infected or had died. Among all children, the estimated cumulative risks of HIV-1 infection or death at ages 6 weeks and 24 months in the zidovudine group were 17.1 and 26.8%, respectively, compared with corresponding risks of 28.4 and 37.5% in the placebo group. Efficacy estimates were 40% at 6 weeks (95% CI 18−56%) and 29% at 24 months (95% CI 10−43%). Among children born to women with CD4 cell counts less than 500 cells/ml, the risk at age 24 months was 43.6% among 143 children in the zidovudine group (56 infected or dead) versus 49.8% among 142 children in the placebo group (66 infected or dead) (efficacy 12%; 95% CI −15 to 33%). In contrast, among children born to women with CD4 cell counts of 500 cells/ml or greater, the estimated cumulative risks among 180 children in the zidovudine group (24 infected or dead) were 10.0% at age 6 weeks, 11.0% at 6 months and 13.1% at 24 months. The corresponding risks among 184 children in the placebo group (52 infected or dead) were 24.3, 24.3 and 29.5%. The estimated risk difference between treatment arms at age 24 months in this group was 16.4% (95% CI 8.0−24.8%), with zidovudine efficacy estimated to reduce the overall MTCT or death risk by 56% (95% CI 31−72%).

Discussion

This is the first study reporting the 24 month efficacy of an oral maternal short-course zidovudine regimen in reducing MTCT of HIV-1 in African breastfeeding populations. Our analysis demonstrates that these peripartum zidovudine regimens can reduce MTCT of HIV-1 despite prolonged breastfeeding; the median duration of breastfeeding in our three populations was 8 to 19.5 months. In our study, zidovudine therapy reduced the probability of HIV-1 transmission at age 24 months by an estimated 26%. However, at all ages the treatment effect strongly depended on the baseline maternal CD4 cell count. Among children born to mothers with CD4 cell counts of 500 cells/ml or greater, zidovudine was associated with an estimated reduction in HIV transmission risk of 54−60% between the ages of 2 weeks and 2 years, and all of these relative differences were statistically significant. In contrast, among children born to mothers with CD4 cell counts

of less than 500 cells/ml, representing 45% of our populations, the estimated reduction in MTCT risk was at most 23% (at age 2 weeks), and was not significant at any age. Among the latter, the cumulative infection rates at age 24 months in both treatment groups were comparable to those documented in observational studies of breastfeeding women in the absence of interventions to reduce MTCT [15]. Results based on HIV-1-free survival at 24 months were similar. In addition, an examination of our results demonstrates a low risk of PT from mothers with prepartum CD4 cell counts of 500 copies/ml or greater, but a substantial risk from mothers with CD4 cell counts of less than 500 cells/ml. We will analyse the PT risk and its determinants in more detail in a separate report.

Our results confirm that advanced maternal HIV-1 disease is a strong determinant of overall MTCT including PT [16]. Other trials that assessed the efficacy of short-term maternal antiretroviral therapy to reduce MTCT reported an association between lower maternal CD4 cell counts and decreased efficacy [6,8,17,18]. However, this is the first study to find that maternal immunodeficiency is associated with a substantial reduction in the efficacy of a maternal short-course zidovudine regimen. In fact, we found that this efficacy reduction seems to occur with a relatively high maternal CD4 cell count in our population. Our study was not large enough to determine the optimal maternal CD4 cell count for defining high versus low efficacy, but we found little difference in efficacy at age 24 months between women with counts less than 350 copies/ml and those with counts of 350–499 cells/ml.

We based our analysis on the CD4 cell count because maternal plasma viral load data are not currently available for many of the non-transmitting mothers. Although viral load may be a better predictor of transmission probability than CD4 cell count, the CD4 cell count is more often available than viral load in developing countries, and is a key biological parameter of HIV disease progression. In addition, in DITRAME, maternal plasma viral load was strongly associated with MTCT of HIV, but it was not possible to define a viral load threshold that could predict MTCT confidently [19].

Several factors strengthen our conclusions. Both trials were randomized and had prospectively collected data in a methodologically rigorous manner. The treatment groups had similar characteristics at baseline. Losses to follow-up for mothers and children combined did not exceed 6.5% for the estimation of MTCT. For each treatment group, MTCT rates were similar in our three study sites. Finally, the overall transmission rate in the placebo arm was similar to rates found in observational studies [15].

An evaluation of the long-term efficacy of a peripartum antiretroviral regimen to prevent MTCT in breastfeeding women is important because PT could reduce efficacy. If there is substantial PT and the regimen does not prevent PT, long-term efficacy will be less than short-term efficacy. It is also possible that PT would be greater after a regimen of several antiretroviral drugs than after a single drug if the combination regimen results in a higher postpartum viral load than before therapy [20]. Indeed, overall, efficacy appears to be somewhat lower at age 24 months than at 6 weeks in our study. Efficacy was maintained for children born to women with CD4 cell counts greater than 500 cells/ml as a result of a very low risk of PT in both treatment arms (Table 5), but efficacy appears to decrease for children born to women with CD4 cell counts of less than 500 cells/ml as a result of substantial PT in both groups. Efficacy estimates based on HIV-free survival gave similar conclusions.

It is of interest to compare these conclusions with those from other studies of antiretroviral agents to prevent MTCT in African breastfeeding women, but our results suggest that such a comparison requires a knowledge of the distributions of maternal CD4 cell counts. There are two other studies on the use of antiretroviral agents to prevent MTCT with long-term results [17,18].

PETRA, the only other such placebo-controlled trial [17], used three regimens of zidovudine plus lamivudine: during the prenatal, intrapartum and postpartum periods (arm A); during the intrapartum and postpartum periods only (arm B); and intrapartum only (arm C). Because many children died without an HIV test result, HIV-free survival was the endpoint. The cumulative endpoint rates at age 18 months were 26.6% in the placebo group, and 20.7, 24.4, and 25.7% in arms A, B, and C, respectively, none of which were significantly different from placebo ($P \geq 0.07$). As efficacy was demonstrated at age 6 weeks for arms A and B (50 and 34%, respectively), this lack of long-term efficacy was attributed by the authors to PT. Women included in the PETRA trial differed in several ways from those in our trials: a greater proportion had had a C-section, they were more likely to practise artificial feeding, and their median CD4 cell count was approximately 100 cells/ml lower than in our population. So far, the investigators have not reported their findings stratified by CD4 cell count. However, their cumulative endpoint rates in the intervention arms at age 18 months are similar to the corresponding rate of 25.8% (95% CI 20.7–30.8%) in our zidovudine arm.

The other trial with long-term efficacy results, HIVNET 012, was conducted in Ugandan breastfeeding women with a median CD4 cell count of approximately 450

cells/ml [18]. It compared nevirapine versus zidovudine, each given to the mother during labor and to the infant for a few days after birth. The MTCT rate at 12 months was 15.7% in the nevirapine arm, 8.4% less than the 24.1% rate in the zidovudine arm ($P = 0.003$), a 35% reduction in the cumulative transmission rate [21]. Again, no CD4 cell stratum-specific estimates were provided. However, our overall cumulative infection rate at 12 months of 21.8% was similar.

Our findings raise several important issues for future research. It is indeed encouraging to confirm a substantial reduction of MTCT in breastfeeding women with high CD4 cell counts using a short zidovudine regimen. However, reducing significantly both peripartum and postnatal MTCT of HIV-1 remains a challenge in African women with some degree of immune deficiency, bearing in mind the need for simple interventions in resource-poor countries. One possibility is extending the duration of prenatal treatment, e.g. by starting zidovudine before 36 weeks' of gestation. With a median duration of 3 weeks of prenatal treatment in our population, efficacy did not differ with the duration of prenatal treatment, but we could not investigate the effect of prenatal treatment for substantially more than 4 weeks. Lallemant *et al.* [22] in Thailand confirmed that among short-course zidovudine regimens, the longer the prenatal treatment, the higher the efficacy in reducing MTCT. However the problems associated with initiating antiretroviral therapy to prevent MTCT earlier than at 36 weeks' gestation in Africa are unknown. Another option is the combination of zidovudine with other antiretroviral regimens. Although a short course of zidovudine plus lamivudine (evaluated in PETRA) did not show efficacy in Africa, the recent French ANRS-075 therapeutic cohort [23] showed an impressive reduction of MTCT in a non-breastfeeding cohort using a long regimen of the same combination. The DITRAME PLUS ANRS-1201 project in Abidjan, Côte d'Ivoire [24], begun in March 2001, is investigating the combination of peripartum zidovudine and one dose of intrapartum nevirapine. Finally the combination of zidovudine, lamivudine and nevirapine may also be a potent and practical short peripartum regimen that should be assessed.

The high rates of transmission between ages 6 weeks and 24 months among children born to women with lower CD4 cell counts in our study demonstrate that interventions to reduce PT are essential to complete peripartum interventions. Alternatives to breastfeeding are of interest [1], but are not practical everywhere and are still under field evaluation in Africa. Continued antiretroviral therapy for mothers after giving birth, and perhaps also for their infants, should be considered, especially for mothers with lower CD4 cell counts. Although women with CD4 cell counts less than 500 cells/ml in our population did not present with HIV-1-related symptoms, they were highly likely to transmit HIV-1 to their child. In developed countries, a CD4 cell count less than 500 cells/ml is not considered to be an indication for initiating antiretroviral therapy in adults [25,26]. However, a comparative analysis of data from Europe and Africa suggests that HIV-1-infected West African adults with similar percentages of CD4 cells have an absolute CD4 cell count 100–200 cells higher than HIV-1-infected European adults, as a result of hyper-lymphocytosis [27]. Therefore, women with CD4 cell counts less than 500 cells/ml might benefit from continued antiretroviral treatment after delivery, in addition to the potential benefit of reducing PT in a breastfeeding population. Finally, regardless of the antiretroviral regimens chosen to reduce peripartum and PT in Africa, safety must be carefully assessed as it has been in developed countries [28].

The public health implications of our results are important considering the recent WHO/UNAIDS recommendations stating that the safety and effectiveness of all antiretroviral regimens to prevent MTCT of HIV-1 warrant their use beyond pilot projects and research settings in Africa [5]. The cumulative event rate in our zidovudine group is similar to the corresponding event rates in the intervention arms in the PETRA and HIVNET 012 trials. However, apart from the difficulty of comparing rates estimated using different statistical procedures in different populations with different breastfeeding practices, results from the other two trials must be stratified on prepartum maternal CD4 cell counts before any comparison can be made with our results. Therefore, at this time it is not possible to determine which antiretroviral regimen is likely to be most efficacious in preventing MTCT of HIV-1 in breastfeeding African women.

We found that this maternal short-course zidovudine regimen may have little efficacy in African breastfeeding women with somewhat advanced HIV-1 disease, and therefore an unknown efficacy at the individual or population level if the distribution of CD4 cell counts is unknown. It is not yet known whether the same is true for ultra-short regimens of nevirapine and short-course regimens of zidovudine–lamivudine. If efficacy for some or all of these regimens depends on maternal immune status, the WHO/UNAIDS recommendations may need to be updated. While waiting for these research findings, the wide-scale implementation of programmes to prevent MTCT of HIV-1 in Africa should not be delayed as there are already many obstacles to surmount in order to fulfil the recently agreed United Nations target of reducing MTCT by 20% by the year 2005 [29].

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Contributors: V. Leroy was the pooled analysis coordinator, wrote the protocol, supervised the research and analysis, and wrote the manuscript. J. Karon co-wrote the protocol and the manuscript and was in charge of statistical analysis. A Alioum contributed to the protocol and provided methodological expertise. E Ekpini was a coordinator at the Projet RETRO-CI in Abidjan. N. Meda was the coordinator at the DITRAME Bobo-Dioulasso centre. S. Wiktor contributed to the protocol and was a coordinator at Projet RETRO-CI in Abidjan. P. Msellati was the coordinator at the DITRAME Abidjan centre. M. Hudgens provided statistical expertise. A.E. Greenberg provided Projet RETRO-CI direction. F. Dabis was the DITRAME ANRS-049 programme coordinator.

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Appendix

The West Africa PMTCT Study Group is composed of the DITRAME ANRS-049 and Projet RETRO-CI Study Groups:

DITRAME ANRS-049 Study Group

Epidemiology: M. Cartoux, F. Dabis (Coordinator of the DITRAME ANRS-049 project), N. Meda (Coordinator of Bobo-Dioulasso Centre), P. Msellati (Coordinator of Abidjan Centre).

Gynecology–Obstetrics: A. Bazié, B. Dao, R. Likikouet, L. Mandelbrot (Principal Investigator), C. Welffens-Ekra (Principal Investigator).

Methodology and Data Management: L. Dequae-Merchadou, V. Leroy, R. Salamon.

Microbiology: D. Bonard, P. Combe, M. Dosso, L. Gautier-Charpentier, F.D. Ky, A. Ouangré, T. Ouassa, O. Sanou, F. Sylla-Koko, Y. Traore, P. Van de Perre.

Molecular Biology: A.M. Cassel-Beraud, J.B. Kottan, O. Manigart, C. Montcho, C. Rouzioux, A. Simonon, D. Valea, B. You.

Pediatrics: R. Camara, N. Elenga, B. Nacro, F. Tall, M. Timité.

Trial monitoring: G. Gourvellec, O. Ky-Zerbo, V. Noba, R. Ramon, I. Sombié, S. Tiendrebeogo, I. Viho, S. Yaro.

Data and Safety Monitoring Board: J.-F. Delfraissy (President), D. Costagliola, C. Chouquet, B. Bazin, P. Lepage, B. Masquelier, K. Toure Coulibaly.

Projet RETRO-CI

E. Ekpini, M. Kouassi, C. Maurice, B. Monga, J. Nkengasong, R. Odum, T. Roels, S. Toussaint (Abidjan, Côte d'Ivoire), A. Greenberg, J. Karon, E. Lackritz, G. Satten, S. Wiktor (Atlanta, USA).