



HAL
open science

**Infant peri-exposure prophylaxis for 12 months to
eliminate breastfeeding transmission of HIV-1 in Africa.
The ANRS 12174 cohort**

T Tylleskär, N Nagot, C Kankasa, N Meda, J K Tumwine, J G Hofmeyr, M
Mwiya, C Siuluta, H Traore, M Kwagala, et al.

► **To cite this version:**

T Tylleskär, N Nagot, C Kankasa, N Meda, J K Tumwine, et al.. Infant peri-exposure prophylaxis for 12 months to eliminate breastfeeding transmission of HIV-1 in Africa. The ANRS 12174 cohort. Conference on Retroviruses and Opportunistic Infections, Mar 2013, Atlanta, United States. hal-03922070

HAL Id: hal-03922070

<https://hal.science/hal-03922070v1>

Submitted on 4 Jan 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Summary

The efficacy of infant peri-exposure prophylaxis (PreP) to prevent HIV-1 postnatal transmission has never been assessed for the entire recommended period of breastfeeding (12 months).

The ANRS 12174 study is a randomised controlled trial comparing the efficacy and safety of lopinavir/ritonavir versus lamivudine to prevent HIV-1 postnatal transmission in breastfeeding children born to HIV-1-infected mothers not eligible for ART (CD4 count above 350 cells/mL) during breastfeeding (maximum 50 weeks). HIV-uninfected children aged 7 days were randomised for either drug in a 1:1 ratio. Infant HIV-infection status was assessed at week 6, 14, 26, 38 and 50 using HIV-1 DNA PCR. The study has completed enrolment in April 2012 in Burkina Faso, Uganda, Zambia and South Africa. We report the current postnatal HIV-1 transmission rate and HIV-1 free survival in the cohort among children aged 50 weeks or more in July 2012.

By the end of July 2012, of 1273 children enrolled in the trial, 788 were aged 50 weeks or older. During this period, 8 transmissions occurred representing a cumulative transmission rate of 1.1% (95%CI: 0.6-2.2). Interestingly, 6/8 transmissions occurred after 6 months of breastfeeding. Overall, 188 severe adverse events (grade 3 or more, DAIDS classification) and 22 deaths were identified. None were considered attributable to the study drugs. The overall cumulative mortality was 3.0% (95%CI: 2.0-4.5) and HIV-1-free survival was 96.0% (95%CI: 94.3-97.2).

Infant PreP is an efficacious strategy that could contribute to the elimination of HIV-1 transmission by breastfeeding.

Rationale

Based on the goals for 2015 and on results of randomised clinical trials and interventional cohorts (1-10), the WHO presently recommends several options for prevention of HIV transmission to breastfed infants of HIV-infected mothers not eligible for antiretroviral therapy (ART) (i.e. CD4 count > 350 cells/ μ L and WHO clinical stage <3), as follows (11, 12):

Option A – infant peri-exposure prophylaxis (PreP): mothers receive daily zidovudine (AZT) during pregnancy, a single-dose nevirapine at delivery and, lamivudine plus AZT for one week post-partum. Children receive daily nevirapine (NVP) immediately after birth for a minimum of 4 to 6 weeks, until 1 week after all exposure to breast milk has ended.

Option B – maternal triple antiretroviral prophylaxis (ARP): mothers receive ARP as early as 14 weeks of gestation until 1 week after all infant exposure to breast milk has ended.

Option B+ – maternal ART: HIV-infected pregnant women receive lifelong ART, regardless of their clinical or immunological status.

The recommended duration of breastfeeding is 12 months, in order to reduce infant mortality and morbidity due to early weaning (13).

Although **option A** (using either nevirapine or lamivudine) and **B** have both proved efficacious in clinical studies, none has administered any of the recommended prophylaxis beyond 6 months, covering only half of the WHO recommended duration of breastfeeding (12 months) for HIV-1-exposed children.

Similarly, the drug of choice for prophylaxis of breastfeeding transmission of HIV relies only on the comparison between different studies, without direct comparison between drugs. Lopinavir/ritonavir (LPV/r), a protease inhibitor with paediatric formulation, has a greater antiviral activity than nucleoside reverse transcriptase inhibitors or non nucleoside reverse transcriptase inhibitors (14), and a good safety profile in young children (14-16), which makes this drug a good candidate for prophylactic purposes, despite its poor palatability.

We report on the postnatal transmission and mortality rates of WHO option A at one year of age using either LPV/r or lamivudine from an unblinded randomised trial conducted in four African countries: Burkina Faso (Ouagadougou), Uganda (Mbale), Zambia (Lusaka) and South Africa (East London).

Material & Methods

Study design

This cohort report is based on the ANRS 12174 randomised controlled trial (ClinicalTrials.gov Identifier: NCT00640263) comparing the efficacy and safety of prolonged infant PreP with LPV/r (40/10 mg twice daily if <2-4 kg and 80/20 mg twice daily if >4 kg) versus lamivudine (7.5 mg twice daily if <2-4 kg, 25 mg twice daily if 4-8 kg and 50 mg twice daily if >8 kg) to prevent HIV-1 transmission through breast milk in children born to HIV-1-infected mothers not eligible for ART during the full duration of breastfeeding (maximum 50 weeks).

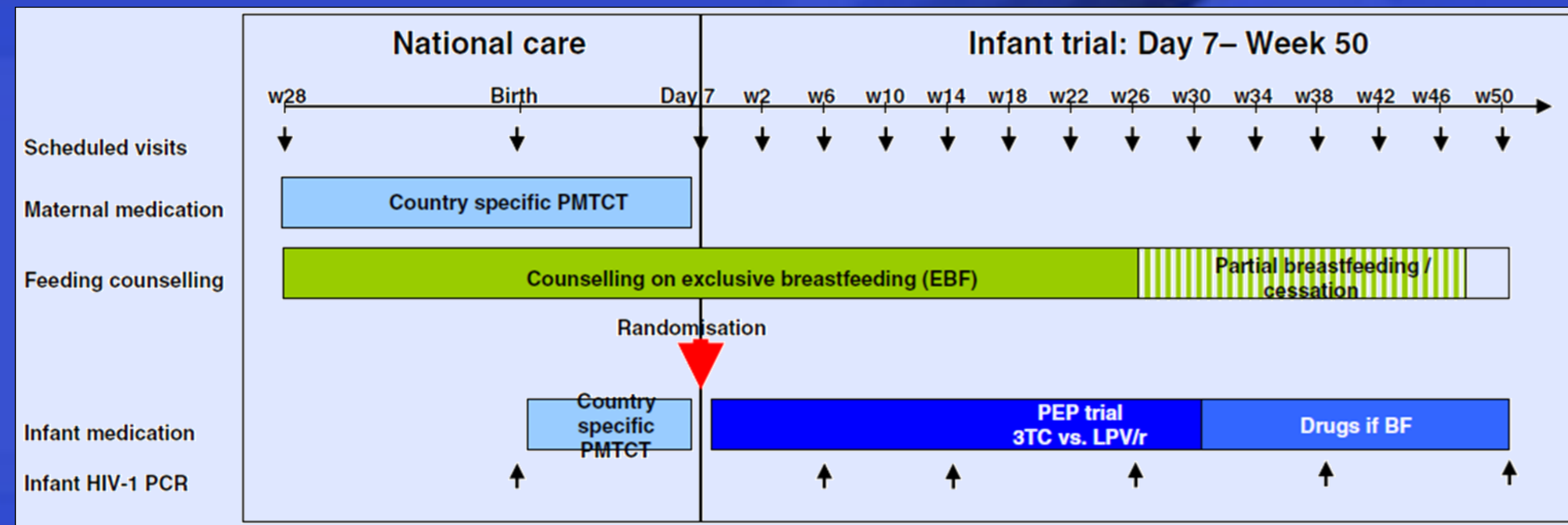


Figure 1. ANRS 12174 Study design. This picture is reproduced from Nagot N, et al., BMC Infectious Diseases, 2012, 12:246

Study

population

Inclusion criteria:

- breastfed at day 7;
- negative HIV-1 DNA PCR test result at day 7;
- had received any PMTCT;
- the mother was HIV-1 infected and was not eligible for ART and was not taking ART.

Exclusion criteria: they presented clinical symptoms and/or biological abnormalities equal to or greater than grade II of the ANRS classification for adverse event on the day of enrolment.

Biological assays

Infant HIV-1 infection was diagnosed on DBS by means of real-time PCR detecting HIV-1 DNA (Generic HIV DNA cell, Bioconfer, France) (17).

HIV-1 infection was confirmed on a second sample by the same technique (18).

Infant peri-exposure prophylaxis for 12 months to eliminate breastfeeding transmission of HIV-1 in Africa

the ANRS 12174 cohort

T. Tylleskär, N. Nagot, C. Kankasa, N. Meda, J.K. Tumwine, J.G. Hofmeyr, M. Mwiya, C. Siuluta, H. Traore, M. Kwagala, A. Sunday, M. Singata, R. Vallo, V. Maréchal, E. Some, D. Rutagwera, D. Neboua, G. Ndeezi, D.

Neveu, D. Jackson, C. Lombard, S. Blanche, H. Sommerfelt, C. Rekacewicz and P. Van de Perre for the ANRS 12174 Trial Group

Results

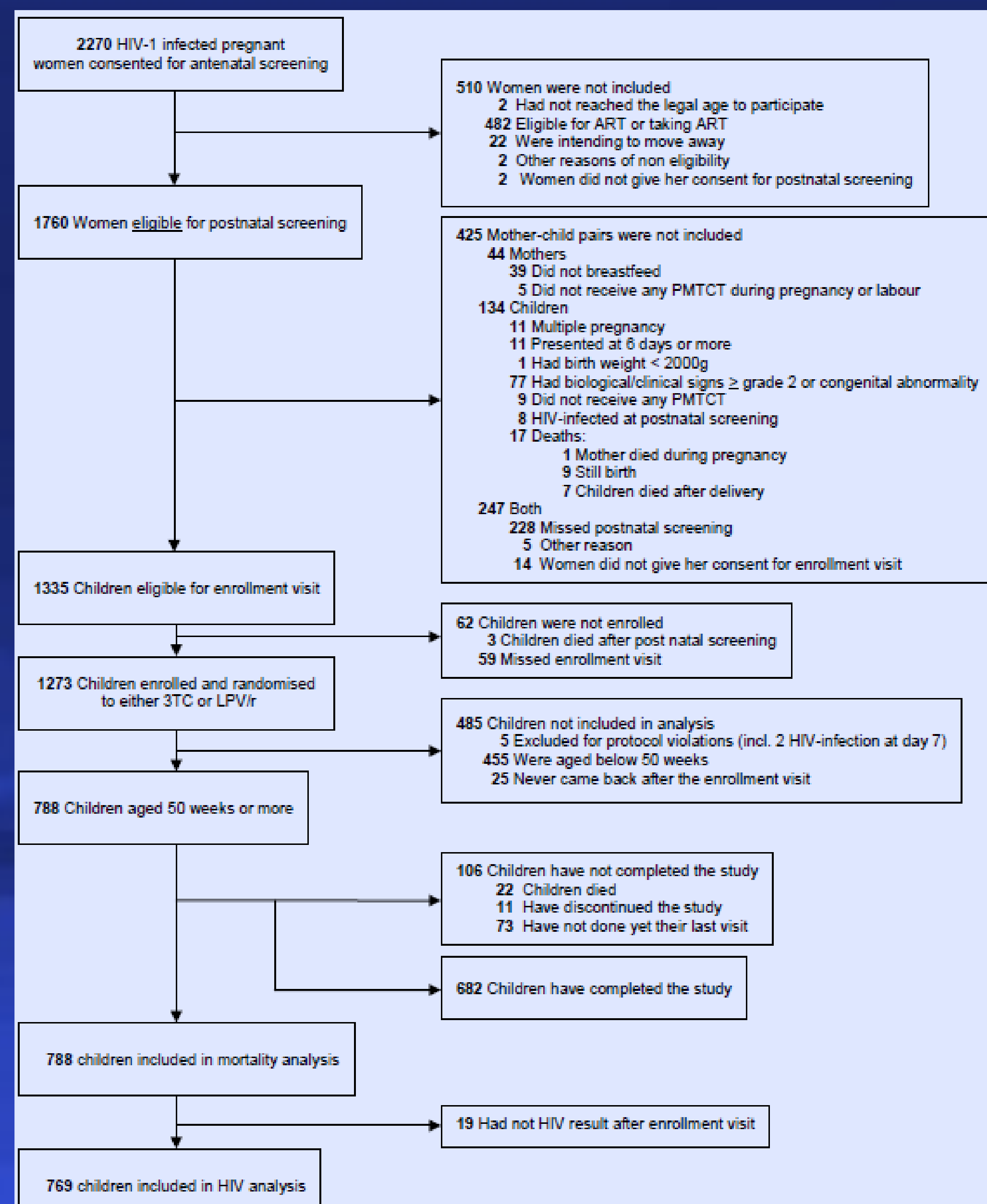


Figure 2. ANRS 12174 cohort profile of infants aged 50 weeks or more on July 23, 2012

Variables	Burkina Faso (n=586)	South Africa (n=105)	Uganda (n=143)	Zambia (n=214)	TOTAL (n=788)
MOTHERS					
Age, mean (SD)	29.3(5.3)	27.9(5.6)	29.5(5.1)	27.3(5.4)	27.9(5.4)
Partly breastfed (SD)	2.8(1.6)	2.6(1.5)	3.4(1.6)	2.7(1.3)	2.8(1.5)
Prophylactic CD4 response count per year	507	629	634	627	507
median (interquartile range)	1628(648)	1628(648)	1628(648)	1628(648)	1628(648)
Plasma HIV RNA (copies/mL)	51 (9.1%)	61 (58.1%)	57 (25.9%)	118 (23.9%)	289 (39.1%)
(log copies per mL)	Mean (SD): 3.1 (0.6)	3.9 (0.7)	3.3 (0.9)	3.5 (0.8)	3.4 (0.8)
Biological HIV staging	158 (99.4%)	102 (99.6%)	131 (99.4%)	272 (99.4%)	761 (97.9%)
Stage I	9 (9%)	3 (3%)	11 (8%)	0 (0%)	23 (3%)
Stage II	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (0%)
Stage III	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Stage IV	0 (0%)	0 (0%)	0 (0%)	2 (1%)	2 (0%)
Unknown staging criteria	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
PMTCT regimen					
During pregnancy	182 (98%)	105 (100%)	108 (99%)	148 (98%)	543 (98%)
During lactation	191 (99%)	104 (99%)	142 (99%)	374 (100%)	711 (99%)
Highest education level completed	None	1 (1%)	9 (6%)	26 (7%)	102 (13%)
Primary	44 (27%)	7 (7%)	88 (66%)	147 (69%)	286 (39%)
Secondary/tertiary	36 (23%)	8 (8%)	48 (36%)	201 (94%)	393 (53%)

Table 1. Baseline (day 7) characteristics of mothers and infants aged 50 weeks or more on the 23rd of July, 2012 in the ANRS 12174 cohort.

References

1. G. S. Chasela, M. G. Hudgens, D. J. Jamieson, D. C. Hosseini, A. P. Kourtis, F. Martinson, G. Tegha, R. Knight, Y. I. Ahmed, D. K. Kamwendu, I. F. Hoffman, S. R. Ellington, Z. Kacheche, A. Soko, J. B. Wiener, S. A. Fiscus, P. Kankasa, I. A. Moko, M. Chigweemba, D. S. Sichihi, C. M. van der Horst. Maternal or infant antiretroviral drugs to reduce HIV-1 transmission. *N Engl J Med* 362: 2271 (2010).
2. H. M. Coovadia, E. R. Brown, M. G. Fowler, T. Chhabra, D. Moody, K. Mavi, D. Marasara, L. Strain-Obanada, V. Chetty, W. Fanai, C. Nankabala, L. Mweh, R. Kusang, L. Govy, A. Masha, D. J. Lynn, S. H. Eastman, P. Richardson, K. George, P. Andrew, L. M. Mofenson, S. Zweriski, Y. Madoondo. Efficacy and safety of an extended nevirapine regimen in infants children of breastfeeding mothers with HIV-1 infection for prevention of postnatal HIV-1 transmission (HPTN 046): a randomised, double-blind, placebo-controlled trial. *Lancet* 379: 221 (2012).
3. D. J. Jamieson, C. S. Chasela, M. G. Hudgens, C. C. King, A. P. Kourtis, D. C. Hosseini, P. D. M. Kamwendu, S. R. Ellington, J. B. Wiener, S. A. Fiscus, G. Tegha, I. A. Moko, D. S. Sichihi, L. S. Adar, R. J. Knight, F. Martinson, Z. Kacheche, A. Soko, I. F. Hoffman, C. van der Horst. Maternal and infant antiretroviral regimens to prevent postnatal HIV-1 transmission: 48-week follow-up of the BAN randomised controlled trial. *Lancet* 379: 2449 (2012).
4. Kesho Bora Study Group. I. de Vincenzi. Triple antiretroviral compared with zidovudine and single-dose nevirapine prophylaxis during pregnancy and breastfeeding for prevention of mother-to-child transmission of HIV-1 (Kesho Bora study): a randomised controlled trial. *Lancet Infect Dis* 11: 171 (2011).
5. C. Kilewo, K. Karlsson, A. Massawa, E. Lyantayo, A. Suali, F. Mhali, O. Biberfeld. Prevention of mother-to-child transmission of HIV-1 through breast-feeding by treating infants prophylactically with lamivudine in Dar es Salaam, Tanzania: the Mitra Study. *J Acquir Immune Defic Syndr* 48: 315 (2008).
6. N. I. Kamwendu, D. R. Hoover, L. M. Mofenson, M. C. Thigpen, G. Kafukula, D. Li, L. Mpanzo, K. Nwansauna, T. Mabrath, M. Buttery, M. G. Fowler, T. E. Taha. Extended antiretroviral prophylaxis to reduce breast-milk HIV-1 transmission.

Breastfeeding

The overall median duration of any breastfeeding was 41 weeks (figure 3)

HIV-1 transmission

8 HIV-1 transmissions have been identified: 5 in Zambia, 3 in Uganda, 0 in Burkina Faso, 0 in South Africa;

→ Cumulative postnatal transmission rate: 1.1% (95%CI: 0.6-2.2);

Interestingly, 6 out of 8 (75%) transmissions occurred after 6 months of breastfeeding, and 2 transmissions occurred within the first six weeks.

A 9th transmission case was detected at 69 weeks after intensive search for a child who never attended any visit since enrolment. Accounting for this case, the HIV-1 transmission rate would become 1.3% (95%CI: 0.7-2.4).

The HIV-1 transmission rate between day 7 and 26 weeks was 0.3% (95%CI: 0.1-1.1).

Among the 1760 mothers potentially eligible in the trial, 1484 of their babies were tested for HIV-1 and 10 were HIV-1 infected (figure 2), giving a perinatal HIV transmission of 0.67%. Therefore, the overall MTCT of full option A was 1.8%, using PMTCT during pregnancy and labour as implemented by national programmes followed by our infant PreP regimens.

Mortality

22 children died: 3 in Burkina Faso, 1 in South Africa, 7 in Uganda and 11 in Zambia;

→ Overall mortality rate: 3.0% (95%CI: 2.0-4.5).

All had a negative HIV-1 DNA PCR test when last tested, on average 7 weeks before death (min: 1 week, max: 35 weeks). No death was deemed attributable to the study drugs.

HIV-1-free survival

Probability for a child to be alive without HIV-1 infection:

• 98.2% (95%CI: 96.9-98.9) at 26 weeks;

• 96.0% (95%CI: 94.3-97.2) at 50 weeks.

At 50 weeks, it was the highest in South Africa (98.9%), and the worst in Uganda (92.7%) (figure 4).

Severe adverse events

Among the 788 children, 188 severe adverse events (88 clinical and 100 biological with no clinical symptoms) had been reported. In April 2012, the Independent DMC recommended continuation of follow-up without unblinding, to the end of the trial (planned in May 2013), considering that these adverse events were not grossly unbalanced between the two arms.

N Engl J Med 359: 119 (2008).

7. C. A. Peller, G. F. Ndayabaya, P. Leppage, J. van Griensven, V. Leroy, C. O. Pharm, P. C. Ndumbari, O. Courtelle, V. Aremu. Breastfeeding with maternal antiretroviral therapy or formula feeding to prevent HIV postnatal mother-to-child transmission in Rwanda. *Aids* 25: 2415 (2011).
8. R. L. Shapiro, M. D. Hughes, A. Ogwo, D. Kilch, S. Lockman, C. Moffat, J. Makhele, S. Moyo, I. Thor, K. McIntosh, E. van Widenfel, J. Leidner, K. Powis, A. Asmelash, E. Tumbare, S. Zweriski, U. Sharma, E. Handelsman, K. Mburu, O. Jayabaya, E. Moko, S. Souda, E. Lubega, M. Ahtar, C. Westler, R. Tonona, W. Snowden, M. Martinez-Tristram, L. Mazhani, M. Esser. Antiretroviral regimens in pregnancy and breastfeeding in Botswana. *N Engl J Med* 362: 2232 (2010).
9. SWEN Study group. Extended-dose nevirapine to 6 weeks of age for infants to prevent HIV transmission via breastfeeding in Ethiopia, India, and Uganda: an analysis of three randomised controlled trials. *Lancet* 372: 300 (2008).
10. T. K. Thomas, R. Masasa, C. B. Borkoof, R. Ndlovu, C. Zhai, A. Masore, J. Osiero, D. Jamieson, M. C. Thigpen, M. Buttery, L. Slutsker, K. M. De Cock, P. N. Anumula, A. E. Greenberg, M. O. Fowler. Triple-antiretroviral prophylaxis to prevent mother-to-child HIV transmission through breastfeeding—the Kisumu Breastfeeding Study, Kenya: a clinical trial. *PLoS Med* 8: e1001015 (2011).
11. WHO. "Antiretroviral drugs for treating pregnant women and preventing HIV infection in infants: recommendation for a public health approach" (WHO, 2010).
12. WHO. "Use of antiretroviral drugs for treating pregnant women and preventing HIV infection in infants - Programmatic update" (WHO, 2012).
13. WHO. "Guidelines on HIV and infant feeding" (WHO, UNAIDS, UNFPA, UNICEF, 2010).
14. E. G. Chadwick, E. V. Capparelli, R. Yogev, J. A. Piro, B. Robbins, J. H. Rozman, J. Chen, P. Palumbo, L. Serchuck, E. Smith, M. Hughes. Pharmacokinetics, safety and efficacy of lopinavir/ritonavir in infants less than 6 months of age. 24

Discussion

First report of the infant PreP strategy during the recommended 12-months duration of breastfeeding with both the lowest postnatal transmission rate (1.1%, 95%CI: 0.6-2.2) and the highest HIV-1 free survival rate (96.0%, 95%CI: 94.3-97.2) ever published.

Combined with mother MTCT, option A allowed an overall MTCT below 2%, well within the target of elimination.

About three-quarters of transmissions occurred after 6 months of age, the time when all previous studies (using either infant PreP or maternal ARP) had stopped antiretrovirals. This stresses the need to obtain complete and valid efficacy data before issuing policy recommendations and choosing between the infant PreP option (A) or the maternal option (B/B+).

Our study had several limitations:

- Although still possible, it is unlikely that some deaths be attributed to undiagnosed HIV-1 infection, given the narrow period since the last HIV-1 negative test.
- All aspects of the infant PreP safety could not be addressed at this stage.
- The drug adherence data have not yet been analysed.

Comparison with maternal antiretroviral prophylaxis (ARP) trials:

In the Kesho-Bora trial, among mothers with CD4 count ≥ 350 cells/ μ L, the 6-month transmission rate, when exposure to breastfeeding stopped, was 4.1% (2.0-8.3%) among mothers with maternal ARP from 28 weeks of pregnancy vs. 5.8% (3.1-10.5%) in the placebo arm (AZT during pregnancy and NVP during labour; infant single-dose NVP at birth and one week AZT after birth). These transmission rates on maternal ARP are four times higher than the MTCT in our cohort at the same time (0.67% perinatal + 0.3% postnatal transmission at 6 months, i.e. 1.0% overall).

The choice of option A or B/B+ to prevent HIV-1 postnatal transmission should be based on robust scientific grounds. Our findings should encourage maintaining infant PreP among the strategic options offered to prevent breastfeeding transmission of HIV-1. As infant PreP, in contrast to maternal ARP, can prevent cell-associated HIV-1 transmission events,(18, 19) it could avert more residual transmission cases than maternal ARP. This could explain the large difference in HIV transmission between the Kesho-Bora trial (maternal ARP) and our study.

Conclusion

The ANRS 12174 study, covering the 12 months of recommended breastfeeding, demonstrated that the infant PreP strategy is an efficacious and safe strategy that could contribute to the elimination of HIV-1 transmission. The identification of the best drug to use for this strategy is the next outcome of this trial.

ANRS 12174 PROMISE PEP

INSERM U1058 *Infection by HIV and by agents with*

mycobacterales tropism: from pathogenesis to prevention

UM1 - UFR de Pharmacie

15 av. C. Flahault - BP 14491

34093 MONTPELLIER Cedex 5

Tel.: +33 4 11 75 96 7778

Fax: +33 4 11 75 97 25

Email: n-nagot@chu-montpellier.fr

