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An optimized strategy triggered at the 2nd immunization visit to prevent HIV acquisition by breastfeeding: a phase 2 trial in Burkina Faso (PREVENIR-PEV)

Anaïs Mennecier[2*], Béninwendé Leticia Delphine Sakana[1], Morgana D'Ottavi[2], Souleymane Tassembedo[1], Jean-Pierre Moles[2], Dramane Kania[1], Ajani Ousmane Taofiki[3], Franck Edgar Kadeba[1], Ibrahima Diallo[1], Sabrina Eymard-Duvernay[2], Nicolas Meda[1], Beatriz Mosqueira[2], Paulin Fao[1], Nicolas Nagot[2], for the PREVENIR-PEV Study Group and Philippe Vande Perre[2]

Abstract

Background Mother-to-child transmission of HIV during breastfeeding remains a challenge in low- and middle-income countries (LMIC). A prevention package was initiated during the highly attended 2nd visit of the Expanded Program of Immunisation (EPI-2) to identify the undiagnosed infants living with HIV and reduce the postnatal transmission of infant exposed to HIV.

Methods PREVENIR-PEV is a non-randomized phase II clinical trial conducted at two health centres in Bobo Dioulasso (Burkina Faso). The study recruited mothers living with HIV aged 15 years and older with their singleton breastfed infants. During EPI-2 (at 8 weeks) and upon signature of the informed consent, a point-of-care early infant diagnosis (EID) was performed. HIV exposed uninfected (HEU) infants were followed-up until 12 months of age. High risk HEU infants (i.e., whose maternal viral load ≥ 1000 cp/mL at EPI-2 or M6) received an extended postnatal prophylaxis (PNP) with lamivudine until end of follow-up or the end of breastfeeding.

Results Between 4 December 2019 and 4 December 2020, 118 mothers living with HIV-1 were identified, and 102 eligible mother/infant pairs had their infants tested for HIV EID. Six infants were newly diagnosed with HIV, and 96 HEU infants were followed-up for 10 months. Among the participants followed-up, all mothers were prescribed antiretrovirals. All 18 infants eligible for PNP at either EPI-2 or 6 months (M6) were initiated on lamivudine. No HIV transmission occurred, and no serious adverse events were reported in infants receiving lamivudine.

Conclusions The PREVENIR-PEV prevention package integrated into existing care is safe and its implementation is feasible in a LMIC with a low HIV prevalence. More research is needed to target mother/infant pairs not adhering to the intervention proposed in this trial.

[†]Anaïs Mennecier and Béninwendé Leticia Delphine Sakana joint first authors.

[†]Nicolas Nagot and Philippe Van de Perre joint senior authors.

*Correspondence:
Anaïs Mennecier
anais.mennecier@inserm.fr
Full list of author information is available at the end of the article

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Keywords Infectious disease transmission, Vertical, Breast feeding, Clinical trial, HIV, Africa, Prevention

Background

Despite the impressive advancements in preventing HIV mother-to-child transmission (MTCT) over the past two decades, progress has plateaued, with at least 130,000 new paediatric infections occurring annually worldwide [1].

In low- and middle-income settings, breastfeeding is recommended for mothers living with HIV to reduce the diarrheal diseases and malnutrition associated with formula milk [2, 3]. Currently, about than half of the paediatric HIV infections occur during breastfeeding [4]. Over the last 20 years, this route of infection has decreased at a remarkably slower rate than that during the perinatal period [5].

Maternal viremia is associated with a higher risk of HIV transmission through breastfeeding [6–9]. Since 2012, lifelong antiretroviral therapy (ART) has been recommended for pregnant or breastfeeding women living with HIV [10] to prevent transmission to infants. However, some pregnant and breastfeeding women do not have access to ART (11% in Burkina Faso in 2020) [11], and those who initiate ART during pregnancy may expose the fetus/infant before maternal viral suppression is achieved. Furthermore, women undergoing treatment may face ART adherence issues [12] and HIV drug-resistance mutations [13]. Suboptimal monitoring of maternal viral load in low- and middle-income countries hampers rapid decision-making regarding HIV management. Infant postnatal prophylaxis (PNP) is internationally recommended to reduce the risk of transmission. It is administered for 6–12 weeks to breastfed infants, depending on their risk of HIV infection (high risk being defined as infants of newly infected mothers or of mothers with a viral load (VL) higher than 1000cp/mL) [14]. Nevertheless, the risk of HIV transmission persists after 6 or 12 weeks and remains unchanged throughout the breastfeeding period [15]. Among the 21 prioritised countries for elimination of MTCT [16], 13 reported an HIV transmission rate $\geq$ 5% during breastfeeding in 2020 [17]. The 5% transmission threshold (including the perinatal and postnatal periods) is an indicator set by the World Health Organization (WHO), wherein a value below this threshold signifies that MTCT was successfully eliminated [18]. Extending the infant's PNP beyond the first three months is currently not recommended internationally [19] because of the research gaps in the benefit and risk balance of this strategy, although this intervention would prevent transmission during the entire exposure.

The PREVENIR-PEV clinical trial aimed to assess the efficacy and safety of a prevention package combining early infant diagnosis (EID), point-of-care (POC) monitoring of maternal viral load, and a single-drug extended PNP in case of maternal viral load higher than 1000 cp/mL, to reduce the risk of post-natal HIV transmission. Because we aimed at evaluating an intervention with a maximum of efficacy at the population level, we screened the newborns at the second visit of the expanded program on immunization (EPI-2). This visit was selected because it was attended by 95% of Burkinabè infants in 2020 [20], captured most of the home deliveries and the incident mothers of the early post-partum period. Furthermore, at this visit, almost no infant born to HIV-infected mother had yet been tested for HIV infection [21].

Methods

Study setting

PREVENIR-PEV was conducted in Burkina Faso, where the UNAIDS estimated HIV prevalence in women 15–49 and MTCT rate were 0.7% and 14.7% in 2022, respectively [11]. At the time of this study, maternal viral load and early infant diagnosis were routinely carried out using central laboratory facilities. The national PNP consisted of a nevirapine regimen administered at birth to all newborn to HIV-infected mother for 6 weeks without adjustment for different high-risk statuses. Infants following the national program had no longer access to a PNP after 6 weeks.

Study design, participants, and intervention

PREVENIR-PEV is a phase II non-randomized clinical trial with one intervention arm and no comparative arm. Participants (mother/infant pairs) were recruited between 4 December 2019 and 4 December 2020. Eligible participants were mothers living with HIV-1 aged 15 years or older, breastfeeding their singleton infants, and attending the EPI-2 visit. Non-eligibility criteria included the intention to move out of the study area, infants with severe congenital malformation, any grade 3 or 4 clinical symptoms, or a known allergy to the study drug (lamivudine).

Maternal HIV status was assessed during the EPI-2 visit to one of the 20 urban health and social promotion centres (CSPS, primary care) in Bobo-Dioulasso.

An HIV test was performed if the previous test was dated back three months or more. After signing the consent form at the CSPS, eligible mother-infant pairs were referred to one of two level 2 referral health centres (CMA of Do or Dafra), to rapidly initiate the trial intervention (i.e. "PREVENIR-PEV prevention package"). A POC EID (Xpert® HIV-1 Qual, Cepheid, Sunnyvale, USA) was performed on neonates' capillary blood. Results were obtained on the same day. Infants with positive results were readily referred to the national program HIV clinic (CMAs) for confirmation of the HIV diagnosis and prompt ART initiation. Those infants did not undergo subsequent follow-up visits in PREVENIR-PEV trial.

Infants with negative HIV test results were eligible to continue their follow-up in PREVENIR-PEV trial. In these cases, a questionnaire was administered to mothers comprising questions on sociodemographic data, medical history, PNP received by the infant at birth, and maternal ART, while the infants were clinically assessed (see questionnaires in the Supplementary materials). Maternal VL was quantified (Xpert® HIV-1 Viral Load, Cepheid, Sunnyvale, USA) and the HIV exposed uninfected (HEU) infants of mothers with a VL ≥ 1000 cp/mL were considered at high risk for HIV acquisition during breastfeeding. During the EPI-same visit, these infants received generic lamivudine oral solution (7.5 mg twice daily if the weight of the infant ranged from 2–4 kg, 25 mg twice daily if 4–8 kg, and 50 mg twice daily if > 8 kg) until 12 months of age or until 1–2 months after breastfeeding cessation (defined as two consecutive monthly visits in which the mother declares having ceased breastfeeding). Furthermore, mothers were encouraged to report the results of their VL test to the physician at their usual HIV outpatient clinic for further management in accordance with national guidelines. Participants on lamivudine attended monthly visits for drug refills, during which study drug adherence (based on questions to mothers), baby weight, and any adverse events were assessed. Infants born to mothers with a VL < 1000 cp/mL were not considered at high risk and therefore did not receive lamivudine therapy had their next follow-up visit at M6.

The M6 follow-up visit included administering of questionnaires on infant nutrition, maternal ART, and a physical examination of the infants. All infants had an HIV diagnostic test, and all mothers a viral load measurement, both using POC Xpert® tests. Infants of mothers with newly unsuppressed VL (VL ≥ 1000cp/mL) initiated lamivudine and were subjected to monthly visits up to the final visit (M12) or until 1- to 2- months after breastfeeding cessation.

Adverse events were only reported for infants on lamivudine based on anamnesis and clinical examination. Serious adverse event related to the study procedures were reported for all participants (mothers and infants).

All participants had an end-of-study visit when the infant was 12 months old, during which the HIV diagnosis of the infant and maternal viral load monitoring were performed (See Appendix).

Mediators from local community-based organisations and advocacy groups were involved in improving adherence to study visits and the accompanying mother-infant pairs at each visit.

Outcomes

The primary outcome was the rate of new infant HIV-1 infection between 8 weeks (EPI-2) and 12 months of age. The secondary outcome were 1) the proportion of infants diagnosed for HIV for the first time at EPI-2; 2) the rate of serious adverse events among HEU infants receiving lamivudine prophylaxis between the EPI-2 and 12-month visits.

Statistical analysis

The WHO defined an impact target for elimination of MTCT with a transmission rate of 5% in breastfeeding populations and 2% in non-breastfeeding populations [18]. We hypothesized a 2% perinatal transmission rate (up to 2 months) and calculated the sample size based on the threshold of 3% transmission rate for the period of 2 months to 12 months. Assuming no transmission during follow-up and no loss to follow-up, recruiting 88 HIV-exposed-uninfected children would provide 80% power to ascertain a transmission rate below the theoretical value of 3% with a one-sided 2.5% alpha risk.

Descriptive summary statistics are presented using percentages and 95% confidence intervals (CI) for categorical variables and means with their standard deviation or medians with interquartile range (IQR) for quantitative variables, depending on variable distribution. Missing data were omitted from the percentage calculations, but can be calculated by subtracting observations from the denominators.

To calculate the HIV-1 infection rate at M12 and the rate of adverse events, patients lost to follow-up at M12 were omitted from the analysis. A 97.5% CI for the HIV infection rate was calculated using the exact method [22].

Adherence to the lamivudine regimen was defined as the actual time on lamivudine (based on monthly refill and questions to mothers) to the expected time on lamivudine according to the protocol. The latter corresponds to the period starting with the first VL ≥ 1000cp/mL to two consecutive monthly visits in which the mother declares having ceased breastfeeding or the end of trial (date M12 performed, or a theoretical M12 date for those who were lost to follow-up), whichever came first. A

child was considered on PNP if the mother had collected the required bottles at the CMA pharmacy, and if she did not report any major adherence issues (defined as two or more consecutive missed doses).

The period at high-risk of post-natal HIV-infection, was defined *post-hoc* as breastfeeding time for which infants were not protected by PNP despite the last maternal VL measure ≥ 1000 copies/mL. This period censored at the end of breastfeeding, was expressed in years per 100 person-years of breastfeeding. A mother was considered as virally unsuppressed from the first VL ≥ 1000cp/mL until the next VL < 1000cp/mL or censored at the last VL monitoring if lost to follow up. Among the infants with at least one day at high risk, we also calculated mean time in months spent at high risk, with SD, in the presence and absence of lamivudine.

Statistical analyses were performed using Stata 16.1 (Stata Corp., College Station, Texas, USA).

The trial is registered in Clinicaltrials.gov (NCT03869944) on 11 March 2019.

Results

Flow chart & participants' characteristics

In total, 14,176 mothers attending EPI-2 visit were screened for HIV infection. Of the 118 mothers living with HIV-1, 16 did not participate in the study (5 did not meet inclusion criteria, 2 declined to participate, and 9 lost to follow-up between CSPS and CMA) and 6 infants were diagnosed with HIV at EPI-2 (Fig. 1).

In total, 96 mothers living with HIV/HEU infant pairs were followed-up during the trial. At baseline, the median age of the 96 mothers with a HEU infant was 33.2 years-old (IQR:29.0–37.0). One-third (30/96) of the mothers were diagnosed with an HIV infection during or after their last pregnancy. All mothers were receiving ART, including one receiving a dolutegravir-containing regimen. An HIV VL ≥ 1000 copies/mL was measured in 13 mothers (13.5%; [95%CI:7.4–22.0]) with a median of 23,200 cp/mL (IQR:5,000–149,000). The median age of the HEU infant at the time of the EPI-2 visit was 9.6 weeks (IQR:9.1–11.1) and 54% (51/95) were girls. The nationally recommended PNP (nevirapine) was initiated at birth for 95% (90/95) of the infants and 87.4% (83/95) took the prophylaxis for the recommended 6 weeks.

Of the 96 HEU participants, 18 (18.8%) did not attend the final M12 visit (12 were unreacheable or moved to another city and 6 did not come to the visit), leaving 78 mother-infant pairs who completed the study. Mothers lost to follow-up were less likely to have introduced PNP to their infants at birth (for 6 weeks or less) ($p = 0.039$). The other baseline characteristics did not differ (Table 1).

Among the mothers having attended the M12 visit, 83.3% (65/78 [95%CI:73.2–90.8]) were still breastfeeding. No significant differences in characteristics were

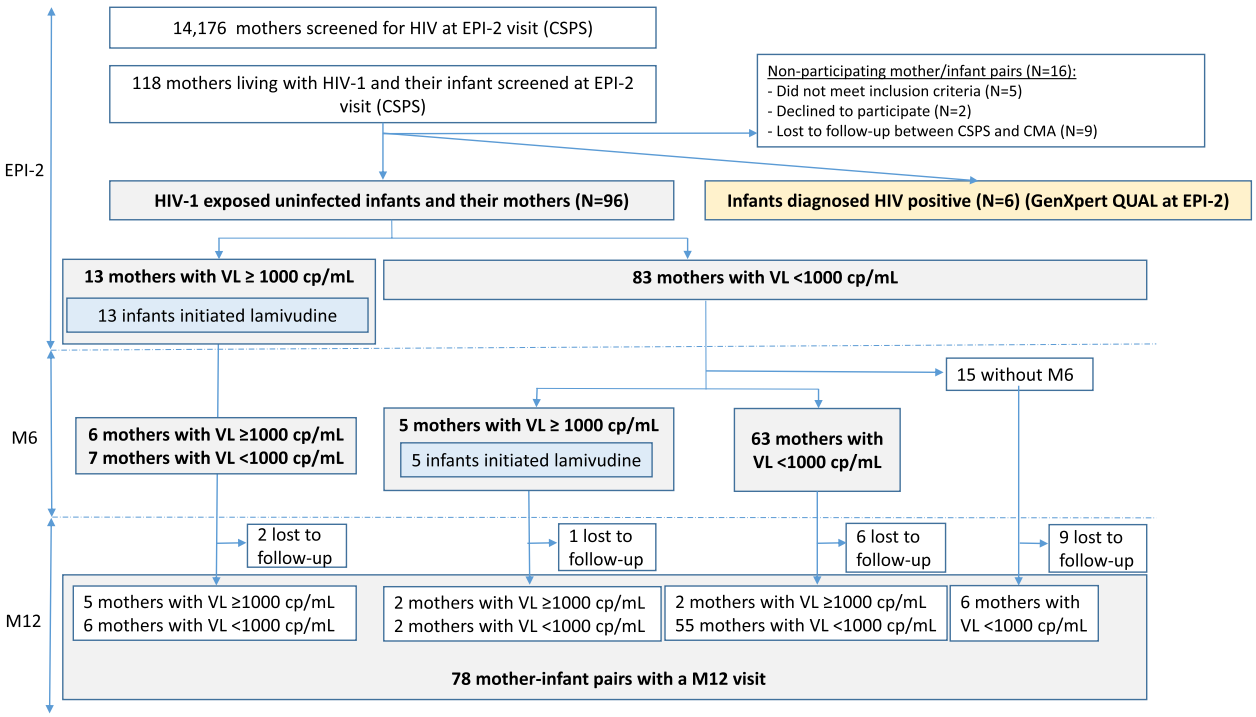

Fig. 1 PREVENIR-PEV Study flow diagram. *CSPS: Health and Social Promotion Centers (primary care). CMA: level 2 referral health centers. VL: Viral load: cp/mL: copies per mililiter*

Table 1 Baseline characteristics for HEU participants with a M12 visit compared to those and lost to follow-up

	Total ($n=96$)	Completed the study ($n=78$)	Lost to follow up ($n=18$)	*p*-value
Mother				
Age (year) (median)	33.2 [29.0–37.0]	32.9 [28.7–37.0]	34.3 [30.8–38.3]	0.26[1]
Parity	3 [2–4]‡	3 [2–4]	3 [2–4]	0.735[3]
Highest education level attended				0.629[2]
None	30 (31.6%)‡	23 (29.5%)	7 (41.2%)	
Primary	37 (39.0%)	31 (39.7%)	6 (35.3%)	
Secondary or tertiary	28 (29.5%)	24 (30.8%)	4 (23.5%)	
Situation during pregancy for this last child				1.000[2]
Not working	63 (67.0%)‡	51 (66.2%)	12 (70.6%)	
Working	31 (33.0%)	26 (33.8%)	5 (29.4%)	
Time to diagnosis				0.413[2]
Before this last pregnancy	66 (68.8%)	52 (66.7%)	14 (77.8%)	
During or after this last pregnancy	30 (31.3%)	26 (33.3%)	4 (22.2%)	
ART (self declaration)	95 (100%)‡	78 (100%)	17 (100%)*	1.000
ART regimen at baseline				1.000[4]
1st line (without dolutegravir)	83 (97.7%)†	69 (97.2%)	14 (100.0%)	
2nd line (without dolutegravrir)	1 (1.2%)	1 (1.4%)	0 (0.0%)	
Regimen with dolutegravir	1 (1.2%)	1 (1.4%)	0 (0.0%)	
Time to ART initiation				0.187[2]
Before this last pregnancy	61 (63.5%)	47 (60.3%)	14 (77.8%)	
During or after this last pregnancy	35 (36.5%)	31 (39.7%)	4 (22.2%)	
Maternal viral load at baseline				0.74[4]
≥ 1000 cp/mL	13 (13.5%)	11(14%)	2 (11%)	
HIV status shared with partner	27 (43.5%)°	25 (46.3%)	2 (35.0%)	0.229[2]
Infant				
Age (days) (median)	9. 6 [9.1–11.1]‡	9. 6 [9.1–11.1]	10.3 [9.3–11.7]	0.300[3]
Weight at baseline (in kg)	5.2 ± 0.9‡	5.2 ± 0.9	5.3 ± 1.1	0.856[1]
Height at baseline (in cm)	58.0 ± 3.4‡	58.3 ± 3.0	56.8 ± 4.5	0.105[1]
Sex (Female)	51 (53.7%)‡	38 (48.7%)	13/17 (76.5%)	0.059[2]
Cotrimoxazole	31 (32.6%)‡	24 (30.8%)	7/17 (41.2%)	0.408[2]
Infants initiating PNP at birth	90 (95%)‡	76 (97%)	14/17 (82%)	0.039[2]

(‡$n=95$,†$n=84$, °$n=62$, *$n=17$) ([1]:Student's t-test, [2]: Fischer's exact test, [3]: Wilcoxon Rank Sum test, [4]: Pearson's chi-squared)

ART Antiretroviral treatment, *PNP* Post Natal Prophylaxis

observed between mothers who stopped breastfeeding before M12 and others (data not shown).

Study intervention

At EPI-2, 8 of the 13-high risk HEU infants were initiated on PNP with lamivudine on the same day of maternal blood collection. Initiation took place within four days for the five remaining infants. At M6, 11 mothers had a VL ≥ 1000 cp/mL, including five who were newly exceeding this threshold. In response, lamivudine was initiated in these five breastfeeding infants (Fig. 1) within a median of 7 days (min–max:1–37).

The mean proportion of days of HIV exposure (breastfeeding) covered by lamivudine was 86.3% (min–max:21.7–100; median: 94.6%. IQR: 81.6%-99.8%).

Primary outcome

Between 8 weeks (EPI-2) and M12, no HIV MTCT occurred (one-sided upper 97.5%CI:4.6) among the 78 children.

Secondary outcomes

Six infants (5.9%; [95%CI:2.2–12.4]) were diagnosed with HIV infection using POC at EPI-2. Two were from mothers diagnosed with HIV at the time of this visit

(VL ≥ 1000 cp/mL at EPI-2), three from mothers with a VL ≥ 1000 cp/mL (629 000cp/mL; 289 000 cp/mL; 29 300 cp/mL at EPI-2) even though they reported being on ART, and one from a mother diagnosed with HIV before this pregnancy, with a VL of 64 cp/mL at EPI-2. Only one of these six infants initiated nevirapine prophylaxis at birth (maternal viral load at EPI-2: 289 000 cp/mL), and none were diagnosed before EPI-2. All but one of the infants were initiated on ART on the day of diagnosis.

No serious adverse events or adverse reactions were reported during this trial among the infants receiving lamivudine.

Post-hoc analysis

The cumulative time at high-risk, standardized to 100 person-years of follow-up, was 1.38 years [95%CI:1.24–1.53] for all HEU infants. Among infants at high risk, mean duration of the high risk period was 1.3 months (SD 2.8). Had lamivudine not been dispensed (as per national guidelines), 1) the cumulative time at high-risk would have been of 12.3 years [95%CI:11.9–12.7] for this given follow-up period, 2) a mean duration of the high risk period would have been 6.1 months (SD 3.2) among the infants at high risk. Assuming 10–20% post-natal transmission risk during this high-risk period, and the absence of intervention, we would have expected to see one or two infections (10% to 20% for 12.3 years at high-risk for 100PY of follow-up = 1.2 to 2.5). This translates to a total transmission rate of 1.5–3.2% among the 78 infants with the final outcome measure.

Overall, 23.0% (20/87; [95%CI: 14.6–33.2]) of the mothers with at least 2 VL measurements (baseline with M6 and/or M12) had a VL ≥ 1000 cp/mL at least once between EPI-2 and M12. At M12, 11.5% of the mothers (9/78 [95%CI: 5.4–20.8]) had a VL ≥ 1000 cp/mL (median 22,100 cp/mL; IQR: 8,720–106,000).

Of the 15 mothers with at least one VL ≥ 1000 cp/mL at EPI-2 or M6 and followed until M12, 9 (60%) had a subsequent VL < 1000 cp/mL without having changed ART regimen.

Discussion

In its March 2021 guidelines, WHO recommends considering re-initiation of PNP for breastfed infants with a maternal VL ≥ 1000 cp/mL, albeit not presenting a level of evidence [23]. In the July 2021 consolidated guidelines, the formal recommendation were recalled, but the WHO acknowledged that some countries recommend extended PNP [19]. Our trial provides, the first scientific evidences on how and to whom to extend the PNP, and has provided the preliminary data justifying a phase III trial [24]. The PREVENIR-PEV prevention package includes the immediate initiation of a single-drug PNP (lamivudine) for confirmed HEU infant in case of maternal viral load ≥ 1000 cp/mL measured using POC machine. With an HIV MTCT rate of 0% [97.5%CI:0.0–4.6] between EPI-2 to 12 month of age, the strategy proved efficacious for the participant retained in care. Nevertheless, the large confidence interval included the 3% postnatal infection rate hypothesized for a given breastfeeding period. This was due to the lower number of HEU participants than expected [21] and the high rate of loss to follow-up. Just over half of the mothers attending EPI-2 were screened for HIV [21]. This low recruitment is mainly due to the heavy constraints associated with conducting a clinical trial [21], and would probably be much lower if the intervention were implemented routinely. Unanswered calls and visits deemed considerably long or distant (especially when the HIV status was not shared with the partner) were the most common reasons for not attending the final M12 visit. Although lost to follow-up mothers were less likely to have introduced PNP in their infants at birth, the proportion of mothers with unsuppressed viral load at baseline was not significantly higher among the mothers who did not attend M12. The children not retained in care would therefore not be at any greater risk.

We observed a perinatal HIV transmission rate of 5.9% at the EPI-2 visit. None of the infants had been previously diagnosed in the national program. Failure to diagnose infants early, mainly due to a lack of sample collection and prolonged turnaround times, has already been identified in Burkina Faso [21]. The infants diagnosed with HIV at EPI-2 in our study had particularly poor compliance with the national prevention of MTCT activities, with maternal VL ≥ 1000cp/mL and no infant prophylaxis initiated at birth in five out of six cases. This perinatal infection rate exceeds the paediatric WHO indicator for elimination of HIV MTCT, which is set at 5% in breastfeeding settings. Without our post-natal intervention, the breastfeeding period would definitely have increased this rate, suggesting that intensification of care and prevention in both the prenatal and postnatal periods is needed nationwide. The PREVENIR-PEV prevention package, with an adherence to lamivudine regimen close to 90%, helped reduce the high-risk period by a factor of nine over the course of the trial, thereby making a major contribution to reducing the rate of postnatal transmission.

At baseline, all mothers of HEU infants and 3 of the 6 mothers of infants diagnosed with HIV declared being on ART. This figure is higher than the 89% ART coverage among pregnant women estimated by the UNAIDS in 2020 in Burkina Faso [11]. Despite an excellent declarative ART coverage, nearly a quarter of mothers of HEU infants (23.6%) had an unsuppressed VL (≥ 1000cp/mL) at least once out of 2 to 3 tests performed during the trial.

Lack of adherence can be considered as the reason for the high VL in 9/15 mothers, as previously described in other settings [13, 25]. These nine mothers regained viral suppression during the trial, after reinforcement of observance and without having changed the ART regimen.

PNP intervention is safe, with no serious adverse event or adverse reactions reported among infants on lamivudine. This is consistent with previous reports from the ANRS 12174/PROMISE-PEP trial in which lamivudine was administered as a PNP to 636 infants from D7 to 50 weeks postnatal [26].

This trial has several limitations. First, although unrestrictive eligibility criteria enabled the majority of the screened participants to be enrolled, nine out of the 118 HIV infected mother-HIV exposed infant pairs were lost to follow-up between recruitment at the CSPS and the beginning of the trial activities at the level 2 centre (CMA). The centralisation of activities necessary to perform the POC diagnostic strategy may have resulted in the attrition of mothers who were the most at risk of transmission. Second, the primary endpoint was measured at 12 months of age, which does not encompass the entire breastfeeding period, as 83.3% of the babies were still breastfed at 12 months. Full coverage of the at-risk period, including late breastfeeding with PNP, should also be considered as a comprehensive strategy. Last, determining the impact of the prevention package on maternal HIV follow-up was not possible in this trial, which is based on children's follow-up.

Conclusion

The PREVENIR-PEV package of intervention was offered to nearly the entire targeted population through its introduction at the EPI-2 visit. It has proved feasible and safe in low- and middle- income settings with a low HIV prevalence. The results of this trial complement those of the phase III efficacy trial (PROMISE-EPI), which was mainly carried out in settings with a high prevalence of HIV [27].

While beneficial for participants who remained in care, the intervention was not adapted to the medical follow-up needs of all mothers living with HIV and their infants, as shown by the trial lost to follow-up rate. Further research is warranted to focus on mother/infant pairs who do not adhere to the PREVENIR-PEV intervention.

Abbreviations

ART Antiretroviral therapy
CMA Level 2 referral health centres
CSPS Urban health and social promotion centres
EID Early infant Diagnosis
EPI-2 2Nd visit of the Expanded Program of Immunisation
HEU HIV Exposed Uninfected
MTCT Mother To Child Transmission
PNP Post-Natal Prophylaxis
POC Point-Of-Care
VL Viral Load
WHO World Health Organization

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

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PREVENIR PEV Study Group

PCCEI/INSERM U1058/University of Montpellier (France): Philippe Van de Perre (principal investigator); Nicolas Nagot (methodologist); Jean-Pierre Moles (international laboratory coordinator); Anaïs Mennecier (global project manager from October 2019); Beatriz Mosqueira (global project manager until September 2019); Morgana D'Ottavi (central data-manager and biostatistician); Sabrina Eymard-Duvernay (central data-manager and biostatistician); Marianne Peries (central data-manager and biostatistician); Vanessa Daoudi (chief administrative officer).

Centre Muraz (Burkina Faso): Paulin Fao (principal investigator); Béninwendé Leticia Delphine Sakana (project manager and monitor); Souleymane Tassembedo (monitor); Dramane Kania (laboratory coordinator); Ajani Ousmane Taofiki (monitor); Edgar Franck Kadeba (assistant laboratory coordinator); Ibrahima Diallo (data manager); Abdramane Berthé (social scientist coordinator); Lalla Sanou (social scientist researcher); Amélie Nikiema (investigator); Emmanuel Coulibaly (investigator); Karim Savadogo (study nurse); Sy Traore (study nurse); Seydou Otore (laboratory technician); Moussa Sinare (laboratory technician); Idrissa Ouedraogo (pharmacy dispenser); Alassane Ouattara (pharmacist); Christine Kafando (patient representative).

Université de Ouagadougou (Burkina Faso): Nicolas Meda (methodologist).

Centre Hospitalier Universitaire Sourô Sanou, Bobo-Dioulasso (Burkina Faso): Makoura Traore/Barro (external expert of the Scientific Advisory Board); Adama Dembele (external expert of the Scientific Advisory Board).

Organisation Ouest Africaine de la Santé Bobo-Dioulasso, (Burkina Faso): Issiaka Sombie (external expert of the Scientific Advisory Board).

World Health Organization: Nigel Rollins (external expert of the Scientific Advisory Board).

School of Public Health, Harvard University (USA): Roger L. Shapiro (external expert of the Scientific Advisory Board).

London School of Hygiene and Tropical Medicine, London (United Kingdom): Melissa Neuman (DSMB chair).

University of Toulouse III (France): Valeriane Leroy (DSMB member).

Assistance Publique – Hôpitaux de Paris (France): Albert Faye (DSMB member).

Centre Hospitalier Universitaire de St Etienne (France): Thomas Bourlet (DSMB member).

South African Medical Research Council (South Africa): Ameena Goga (DSMB member).

Kwame Nkrumah University (Zambia): Connie Osborne (DSMB member).

ANRS-MIE (France): Laura Fernandez (project manager).

Authors' contributions
PVdP and PF: coordinating investigators. PVdP, NN, JPM, NM: study conception, planning and design. PVdP, NN, JPM, BM, BLDS and PF: preparation of the final version of the protocol. AM, BM, BLDS and ST: study management. PF, DK, BLDS, ST and AOT: field coordination. DK and FEK: lab coordination. NN, MD, AM, SED and ID: data management and analysis. AM: drafting of the manuscript. PVdP, NN, JPM and MD: editing the manuscript. All authors significantly contributed to the manuscript and approved the final version of the manuscript.

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Availability of data and materials
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The trial was approved by the Centre Muraz Ethics Committee (reference number:33) and the Ethics Committee for Health Research (CERS, number 2017–9-144) of Burkina Faso.
A Data Safety Monitoring Committee monitored the trial until completion. Informed consent was obtained from all the participants and from the legal guardians of the participants who were below 16 years of age.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Infectious Disease Research Programme, Centre MURAZ/National Institute of Public Health, Bobo-Dioulasso, Burkina Faso. [2]Pathogenesis and Control of Chronic and Emerging Infections, Montpellier University, INSERM, 60 Rue de Navacelles, Montpellier, EFS 34394, France. [3]Sexual and Reproductive Health Research Programme, Centre MURAZ/National Institute of Public Health, Bobo-Dioulasso, Burkina Faso.

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