HIV-1 disease progression in immune-competent HIV-1-infected and breastfeeding mothers participating in the ANRS 12174 clinical trial in Burkina Faso, South Africa, Uganda and Zambia: a cohort study

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ABSTRACT

Objective We have assessed HIV-1 disease progression among HIV-1-positive mothers in relation to duration of any or exclusive breast feeding in the context of ANRS 12174 trial.

Methods The analysis was completed on 203, 212, 272 and 529 HIV-1-positive and lactating mothers with CD4 count >350 cells/µL from Burkina Faso, South Africa, Uganda and Zambia, respectively. The trial compared lamivudine and lopinavir/ritonavir as a peri-exposure prophylaxis during a 50-week follow-up time. A multiple logistic regression model was run with the mothers' weight, CD4 count and HIV-1 viral load as separate dependent variables, then combined into a dependent composite endpoint called HIV-1 disease progression where HIV-1 viral load was replaced by the HIV-1 clinical stage. Exclusive or predominant breast feeding (EPBF) and any breastfeeding duration were the key explanatory variables.

Results In the adjusted model, the associations between EPBF duration and weight change, CD4 cell count and the HIV-1 viral load were consistently insignificant. The CD4 cell count was associated with a significantly higher mothers' body mass index (BMI; a mean increase of 4.9 (95% CI 2.1 to 7.7) CD4 cells/µL per each additional kilogram per square metre of BMI) and haemoglobin concentration (19.4 (95% CI 11.4 to 27.4) CD4 cells/µL per each additional gram per decilitre of haemoglobin concentration). There was no significant association between EPBF duration and HIV-1 disease progression. A higher education level was a factor associated with a slower HIV-1 disease progression.

Conclusion Breast feeding was not a risk factor for a faster progression of HIV-1 disease in mothers of this cohort with a baseline CD4 cell count >350 cells/µL.

Trial registration number NCT0064026; Post-results.

Strengths and limitations of this study

- Our study has been implemented in four countries in Africa, namely Burkina Faso (West), South Africa and Zambia (South), and Uganda (East), which made our sample representative of the wider sub-Sahara African population.
- The data were collected in the context of a rigorous clinical trial, which minimised the loss to follow-up, the missing data as well as other data collection errors, and therefore improved the quality of our data.
- However, the selection associated with the environment of a clinical trial, usually quite different from a routine environment, may have biased our findings.
- Nonetheless, the variables analysed separately as dependent variables or as part of our composite endpoints (mother's weight, CD4 cell count, HIV-1 viral load or HIV-1 clinical stage) were sufficiently robust and had a high validity.

INTRODUCTION

In 2015, 36.7 (34.0–39.8) million people were infected with HIV. Among them, 17.4 (16.1–20.0) million were women of childbearing age.[1 2] HIV-1 prevalence was estimated between 5.3% and 6.5% among pregnant women in sub-Saharan Africa.[3] Because of the almost irreversible immune activation involved, HIV-1 infection creates a condition of metabolic stress that may result in wasting and immune depression.[4–7] Ten per cent weight loss and a CD4 count of <350 cells/µL in the context of HIV-1 infection have been recognised as major criteria of the diagnosis of AIDS.[8] This weight loss is also associated

with a higher risk of mortality in HIV-1-infected breastfeeding mothers.[9] Furthermore, HIV-1 is a major cause of maternal mortality in affected countries in Southern Africa. About 25% of pregnancy-related deaths in sub-Saharan Africa are attributable to HIV,[10] and 88% of deaths among pregnant and postpartum women with HIV infection are attributable to the virus.[11]

In women, pregnancy is, though a physiological condition, a period of increased metabolic activities and synthesis requiring a supplement of energy and nutrients. After delivery, breast feeding prolongs the increased metabolic demands. Despite this, WHO still recommends HIV-1-infected women to breast feed as the best choice for the infant and the mother[12] in contexts where replacement feeding does not meet AFASS (affordable, feasible, available, safe and sustainable) criteria.

There have been conflicting results on assessment of the impact of breast feeding in HIV-1-infected mothers. Some studies found that breast feeding was harmful to HIV-positive mothers by either accelerating HIV disease progression as assessed by the mother's weight loss, a decrease in CD4 cell count or even an increased risk of maternal mortality, suggesting that metabolic, immunological or hormonal changes associated with breast feeding may accelerate HIV-1 disease progression in postpartum mothers.[13–15] Others found no effect on the mothers' health assessed by death, development of a low CD4 cell count, anaemia or excessive weight loss.[16 17] Some studies have found breast feeding protective, allowing weight gain in HIV-1-infected breastfeeding mothers.[15 18–22]

In the ANRS 12174 trial, we assessed mothers' HIV-1 disease progression (measured by the change in weight, CD4 cell count and HIV-1 disease stage as per WHO classification) in relation to exclusive breast feeding or duration of any breast feeding during the infant first 6 months of life and until week 50 post partum.

METHODS

Study design

The ANRS 12174 clinical trial in Ouagadougou (Burkina Faso), East London (South Africa), Mbale (Uganda) and Lusaka (Zambia) was conducted from 2009 to 2013. The protocol and the main outcome have been published.[23 24] Briefly, a cohort of HIV-1-infected, pregnant women, at the time not eligible for highly active antiretroviral therapy because CD4 count was >350 cells/µL, aged 18 or above and planning to breast feed were identified from antenatal clinics between 28 and 40 weeks of amenorrhoea. As part of the HIV post-test counselling session, they were informed on the different feeding options for their babies. Only women intending to breast feed were referred to the research clinic for further assessment of the inclusion criteria during the antenatal period and again with their child within 6 days after birth, for an enrolment and randomisation at day 7 post partum. From 28 weeks of pregnancy to day 7 after birth, programmatic mother-to-child transmission prophylaxis was implemented with antepartum zidovudine, intrapartum single-dose nevirapine and zidovudine–lamivudine for mothers and nevirapine for infants for 7 days postpartum. Twins and triplets, infants with positive HIV-1 DNA PCR test result at day 7 (±2 days) post partum, low birthweight or ill babies (ranked grade II or above of the ANRS classification for adverse events) were excluded.[25] The intervention provided an infant prophylaxis in the breastfeeding period plus 1 week from day 7 to 50 weeks of age with either lopinavir/ritonavir or lamivudine.

Data management and analysis

Data were collected on a paper case-report form or directly entered online using the Electronic Data capture system: OpenClinica (http://www.openclinica.com). Twenty-four-hour and 1-week breastfeeding recalls were collected during the enrolment visit at day 7±2 days after birth and the 13 monthly scheduled follow-up visits that started at week 2. During these visits, mothers were asked in particular if they gave their infants other foods/liquids as well as breast milk. Prelacteal feeding data—

defined as any food item except mothers' milk given to infants before initial breast feeding—were also collected at the enrolment visit.

The mothers at each visit were categorised into the following groups: (1) exclusive breast feeding, EBF (only breast milk being given to the infant without any other food or liquid, except medically prescribed drugs or vitamins); (2) predominant breastfeeding, PBF (breast milk with some liquid-based food, such as juice, tea, sugar water and salt water, including glucose without any kind of formula, or animal milk); and (3) mixed feeding, MF (breast milk with other solid-based or liquid-based food, including other kinds of milk). We thereafter combined EBF and PBF into one group called 'exclusive or predominant breastfeeding' (EPBF) as PBF presented few cases and was assessed as having much the same risk as EBF, at least with regard to postnatal HIV transmission.[26]

During the follow-up visits, the mothers underwent a clinical assessment, including weight measurement and HIV-1 infection staging at the first screening visit or screening one (between 28 and 40 weeks of gestation), day 7 post partum, weeks 26 and 50; CD4 cell count analysis at screening one, weeks 26 and 50; and HIV-1 viral load at screening one, day 7, weeks 6, 14, 26, 38 and 50. The dependent variables were mothers' weight, CD4 cell count and HIV-1 viral load considered separately and measured at the same time points as per above. We generated a new variable called 'weight loss', which was calculated as the mothers' weight at W26 (because of missing data, mothers' weights were not available for week 50) minus the baseline weight at day 7 post partum, which was compared with the baseline weight to assess if the loss had reached 10%. Furthermore, we combined CD4 cell count, mothers' weight loss and HIV-1 disease stage as per WHO classification to create the composite endpoint called 'HIV-1 disease progression'. HIV-1 disease progression was

accelerated when CD4 cell count decreased to <350 cells/µL, or the HIV-1 infection was assessed by the trial physician at stage 3 or above, or the mothers lost >10% of their weight; otherwise, HIV-1 disease progression was deemed absent or slow. Our main independent variable was EPBF (until week 26 post partum) or any breastfeeding (until week 50 post partum) duration. The data were collected by trained physicians, pharmacists, biologists and counsellors. Seca-brand scales and stadiometers were used to measure the mother's height and weight. Weights were rounded to the nearest 10 g and the height to the nearest millimetre. Weight and height were measured twice based on the WHO guidelines (http://www.who.int/childgrowth/training/en/).

We first ran linear mixed-effect models that considered separately the mothers' weight, CD4 cell count and HIV-1 viral load changes as dependent variables, and EPBF or any breast feeding as key independent variables. The loss to follow-up were censored in a survival analysis completed to build the EPBF and any breastfeeding variables.[27] When the inter-country variability was not significant, a linear multivariate regression analysis was run. We ran a logistic regression regarding the composite endpoint. Adjustment covariates included baseline variables measured at the screening one visit (body mass index (BMI), education level, marital status, haemoglobin concentration) or on day 7 post partum (mode of delivery, breastfeeding initiation time, the baby's gender and the trial arm). These multivariate analyses were run taking all participants together and also as two strata comprising South African mothers (stratum 1) and Burkina Faso, Uganda and Zambia together (stratum 2) because South Africa presented important socioeconomic, cultural and demographic differences compared with the other countries. For continuous variables, the mean values with 95% CI were estimated, and for categorical variables, percentages were used. Associations between variables were tested using the χ^2 test for categorical variables. STATA/SE V.13.1 statistical software has been used for the analyses.

Ethics

Prior to enrolment, the mothers signed a written informed consent and assent forms for themselves and their children, respectively. The trial was conducted according to the sponsor (ANRS) ethic charter, Good Clinical Practices and the principles of the Helsinki declaration.

RESULTS

In the ANRS 12174 trial, 1273 mother–infant pairs were randomised and six were excluded due to protocol violations. Of the remaining 1267 participants, 204 were from Ouagadougou, 222 from East London, 278 from Mbale and 563 from Lusaka. In all, 42 were excluded from analysis due to lack of breastfeeding data after inclusion, 7 due to inaccurate feeding duration data and 2 women had no data on weights. The analysis included 1216 subjects. The complete flow chart has been published elsewhere.[27] The mean baseline weight, the percentage of educated and employed women was highest, and the mean EPBF

Table 1a Baseline characteristics collected at screening one or on day 7 post partum and breastfeeding duration data (continuous variables)

	Burkina Faso	South Africa	Uganda	Zambia	All sites
	n=203	n=212	n=272	n=529	n=1216
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)
Mean duration of zidovudineregimen post-delivery (days)*	6.6 (6.5 to 6.8)	7 (7.0 to 7.0)	6.8 (6.7 to 6.9)	7.0 (6.9 to 7.0)	6.9 (6.8 to 7.0)
Mean duration of lamivudine regimen post-delivery (days)*	6.6 (6.5 to 6.8)	Data not available	6.7 (6.6 to 6.8)	7.0 (6.9 to 7.0)	6.8 (6.8 to 6.9)
Mean baseline CD4 count×10^2 cells/µL	5.6 (5.4 to 5.8)	5.5 (5.3 to5.7)	5.6 (5.4 to 5.8)	6.0 (5.8 to 6.2)	5.8 (5.7 to 5.9)
Mean baseline viral load×10^3 copies/µL	23.0 (7.3 to 38.7)	13.5 (7.5 to 19.6)	34.9 (19.7 to 50.0)	29.1 (21.5 to 36.6)	26.4 (21.1 to 31.8)
Baseline mothers' weight (kg)	62.9 (61.4 to 64.5)	72.1 (70.0 to 74.1)	58.1 (57.0 to 59.2)	62.0 (61.0 to 62.9)	63.0 (62.3 to 63.7)
Mean EPBF duration (months)	6.3 (6.2 to 6.4)	4.8 (4.7 to 4.9)	5.6 (5.5 to 5.7)	6.0 (5.9 to 6.1)	5.8 (5.7 to 5.9)
Mean breastfeeding duration (months)	10.5 (10.4 to 10.6)	6.7 (6.6 to 6.8)	8.4 (8.3 to 8.5)	8.4 (8.3 to 8.5)	8.4 (8.3 to 8.5)

*AZT and 3TC (zidovudine and lamivudine) are usually administered together. However, in our data collection tool (the questionnaire), the investigators had to ask specifically and separately the question for AZT and 3TC. We suspect that they may have been some reporting errors, creating slight differences in the percentages of women who complied with the prophylaxis requirements.
EPBF, exclusive or predominant breast feeding.

Table 1b Baseline characteristics collected at screening one or on day 7 post partum and breastfeeding duration data (categorical variables)

	Burkina Faso	South Africa	Uganda	Zambia	All sites
	n=203	n=212	n=272	n=529	n=1216
	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)
Mother's age group (years)					
Below 25	26.2 (20.5 to 32.6)	34.4 (28.3 to 41.1)	39.3 (33.7 to 45.3)	37.8 (33.8 to 42.0)	35.6 (33.0 to 38.3)
25–30	36.9 (30.6 to 43.8)	31.2 (25.2 to 37.7)	35.7 (30.2 to 41.5)	33.1 (29.2 to 37.2)	34.0 (31.3 to 36.7)
30 and above	36.9 (30.6 to 43.8)	34.4 (28.3 to 41.1)	25.0 (20.2 to 30.5)	29.1 (25.4 to 33.1)	30.4 (27.9 to 33.1)
HIV stage 1	93.1 (88.7 to 95.9)	98.6 (95.7 to 99.5)	92.3 (88.4 to 94.9)	99.8 (98.7 to 100.0)	96.8 (95.6 to 97.6)
Education					
Did not complete primary school	68.5 (61.7 to 74.5)	8.5 (5.4 to 13.1)	48.5 (42.6 to 54.5)	28.2 (24.5 to 32.2)	36.0 (33.4 to 0.38.8)
Completed primary school	7.4 (4.5 to 11.9)	0.5 (0.1 to 3.3)	15.8 (11.9 to 20.6)	18.5 (15.4 to 22.1)	12.9 (11.1 to 14.9)
Secondary school and more	24.1 (18.7 to 30.5)	91.0 (86.4 to 94.2)	35.7 (0.30.2 to 41.5)	53.3 (49.0 to 57.5)	51.1 (48.2 to 53.9)
Marital status (married)	90.6 (85.8 to 94.0)	39.1 (32.8 to 45.9)	82.0 (76.9 to 86.1)	88.7 (85.7 to 91.1)	78.9 (76.5 to 81.1)
Occupation (employed)	8.9 (5.6 to 13.6)	41.5 (35.0 to 48.3)	35.3 (29.8 to 41.2)	17.0 (14.0 to 20.5)	24.0 (21.7 to 26.5)
Primipara	21.7 (16.5 to 27.9)	33.5 (27.4 to 40.1)	18.0 (13.9 to 23.0)	20.6 (17.4 to 24.3)	22.4 (20.2 to 24.9)
Vaginal delivery	93.6 (89.3 to 96.2)	65.1 (58.4 to 71.2)	93.4 (89.7 to 95.8)	96.2 (94.2 to 97.5)	89.7 (87.9 to 91.3)
Breastfeeding initiation time (within 1 hour)	6.9 (4.1 to 11.3)	51.4 (44.7 to 58.1)	55.9 (49.9 to 61.7)	80.7 (77.1 to 83.9)	57.7 (54.9 to 60.5)
Lamivudine arm	49.7 (42.9 to 56.6)	51.9 (45.1 to 58.6)	49.6 (43.7 to 55.6)	50.3 (46.0 to 54.5)	50.3 (47.5 to 53.1)
Female baby	41.9 (35.2 to 48.8)	49.1 (42.4 to 55.8)	52.9 (46.0 to 58.8)	48.4 (44.1 to 52.7)	48.4 (45.6 to 51.2)

and any breastfeeding durations shortest in South Africa where the HIV-1 viral load was also the lowest (table 1a and b).

Overall, in the adjusted model, the association between EPBF duration and weight change was negative and non-significant. Mothers who completed secondary school had a significant mean increase of 1.1 kg compared with those who did not complete primary school (table 2a).

The association between CD4 cell count and EPBF duration was non-significant (5.4 (95% CI −0.1 to 10.9) and 4.5 (95% CI −6.2 to 15.1) CD4 cells/µL increase per month of EPBF duration at univariate and multivariate analyses, respectively). The association was significantly positive between the mothers' baseline BMI, haemoglobin concentration and CD4 cell count yielding a mean increase of 4.9 (95% CI 2.1 to 7.7) CD4 cells/µL per additional BMI unit and 19.4 (95% CI 11.4 to 27.4) CD4 cells/µL per additional unit of haemoglobin throughout the EPBF period (table 2b).

There was no significant association between HIV-1 viral load and EPBF duration. The heavier and older mothers, those who delivered female babies and the best educated women group had a significantly lower mean viral load in the multivariate analysis. The mothers allocated to the lopinavir/ritonavir group had a significantly higher mean viral load than the ones in the lamivudine arm (table 2c).

We found no significant association between EPBF duration and HIV-1 disease progression. However, randomisation to the lopinavir/ritonavir arm or being a single mother led to a significantly adjusted OR of 1.3 (95% CI 1.0 to 1.6; P=0.04) and 1.6 (95% CI 1.3 to 2.1), respectively (table 2d).

Considering any breastfeeding duration, there was no weight change at univariate and multivariate analyses overall (table 3a). Still regarding any breast feeding, overall, there was a significant mean increase of 5.7 (95% CI 0.4 to 10.9) CD4 cells/µL per month of any breast feeding. We found also that being a single mother was associated with a mean decrease of −43.3 (95% CI −72.8 to −13.7) CD4 cells/µL as compared with married ones (table 3b). Any breastfeeding duration was also associated with a significantly higher mean viral load (table 3c). Analysis with any breastfeeding pattern and HIV-1 disease progression showed the same associations as EPBF and HIV-1 disease progression (table 3d).

Table 2a Mothers' weight change according to EPBF duration adjusted to different covariates: stratification presenting South Africa versus the other sites and pooled analysis

	South Africa		Burkina Faso, Uganda and Zambia		Pooled analysis	
	Unadjusted coefficient (95% CI)	Adjusted coefficient (95% CI)	Unadjusted coefficient (95% CI)	Adjusted coefficient (95% CI)	Unadjusted coefficient (95% CI)	Adjusted coefficient (95% CI)
Dependent variable=mother's weight						
EPBF duration (months)	0.1 (–0.7 to 0.9)	–0.2 (–0.6 to 0.1)	–0.1 (–0.5 to 0.3)	0.1 (–0.0 to 0.3)	–0.2 (–0.5 to 0.2)	–0.1 (–0.2 to 0.1)
Baseline BMI (kg/m^2)	2.5 (2.4 to 2.7)	2.4 (2.3 to 2.6)	2.5 (2.4 to 2.6)	2.4 (2.3 to 2.5)	2.5 (2.4 to 2.6)	2.4 (2.3 to 2.5)
Mother's age (years)	0.8 (0.5 to 1.2)	0.1 (0.0 to 0.3)	0.5 (0.4 to 0.6)	0.1 (0.1 to 0.2)	0.5 (0.4 to 0.7)	0.1 (0.1 to 0.2)
HIV disease stage						
HIV stage 1						
HIV stage >1	12.4 (–4.5 to 29.4)	6.7 (0.4 to 13.1)	–2.8 (–6.4 to 0.8)			
Education						
Did not complete primary school			1	1	1	1
Completed primary school			3.9 (2.0 to 5.9)	0.2 (–0.7 to 1.1)	4.4 (2.2 to 6.5)	0.6 (–0.3 to 1.5)
Secondary school and more			2.7 (1.2 to 4.1)	0.7 (0.1 to 1.4)	3.1 (1.5 to 4.6)	1.1 (0.4 to 1.8)
Marital status						
Married/ cohabiting mothers	1				1	
Single mothers	–3.1 (–7.2 to 0.9)				–1.2 (–3.0 to 0.5)	
Delivery						
Vaginal delivery	1		1		1	1
C-section delivery	3.7 (–0.4 to 7.9)		4.5 (1.5 to 7.6)		4.4 (2.1 to 6.7)	–1.1 (–2.1 to –0.1)
Parity						
Primipara	1		1		1	–
Multipara	6.1 (1.9 to 10.3)		3.1 (1.4 to 4.7)		3.9 (2.3 to 5.4)	–
Trial arm						
Lamivudine arm	1	1	1	1	1	1
Lopinavir/ ritonavir arm	2.0 (–2.0 to 6.1)	0.8 (–0.7 to 2.3)	–0.1 (–1.4 to 1.3)	–0.3 (–0.9 to 0.2)	0.3 (–1.0 to 1.6)	–0.1 (–0.7 to 0.4)

BMI, body mass index; EPBF, exclusive or predominant breast feeding.

In the stratified analysis, we found that EPBF duration had no influence on mothers' weight, CD4 count or HIV-1 viral load, whatever the stratum. HIV-1 disease progression was not associated either with EPBF duration (table 2a, b, c and d). In stratum 2, C-section delivery was associated with an increase in CD4 cell count (table 2b), whereas delivering a female baby and being educated beyond secondary school were associated with a decrease in HIV-1 viral load (table 2c).

In South Africa, initiating breast feeding 1 hour post-delivery and being a single mother were related to an increase in HIV-1 viral load. In both strata, C-section delivery and multiparity were also related to an increase in HIV-1 viral load. There was no association between any breast feeding and the mothers' weight, CD4 cell count and HIV-1 disease progression in any of the strata (table 3a, b and d). However, any breastfeeding duration was associated with an increase of the HIV-1 viral load in South African women (table 3c).

DISCUSSION

Considered separately, there appeared to be no variations in the mothers' weight, CD4 cell count and HIV-1 viral

Table 2b Mothers' CD4 cell count change according to EPBF duration adjusted to different covariates: stratification presenting South Africa versus the other sites and pooled analysis

	South Africa		Burkina Faso, Uganda and Zambia		Pooled analysis	
	Unadjusted coefficient (95% CI)	Adjusted coefficient (95% CI)	Unadjusted coefficient (95% CI)	Adjusted coefficient (95% CI)	Unadjusted coefficient (95% CI)	Adjusted coefficient (95% CI)
Dependent variable=CD4 cell count						
EPBF duration (months)	−1.0 (−8.9 to 7.0)	−6.4 (−18.6 to 5.8)	9.3 (2.3 to 16.3)	7.9 (−4.2 to 20.1)	5.4 (−0.1 to 10.9)	4.5 (−6.2 to 15.1)
Baseline BMI (kg/m^2)			4.9 (2.4 to 7.3)	5.9 (2.5 to 9.2)	3.3 (1.3 to 5.3)	4.9 (2.1 to 7.7)
Mother's age (years)	−3.1 (−7.5 to 1.2)		−4.9 (−7.3 to −2.5)	−6.2 (−8.6 to −3.8)	−4.7 (−6.9 to −2.6)	−6.2 (−8.4 to −4.1)
Haemoglobin concentration (g/dL)	33.3 (12.7 to 53.8)	34.8 (14.4 to 55.1)	15.2 (7.8 to 22.6)	12.9 (4.6 to 21.2)	19.3 (12.3 to 26.4)	19.4 (11.4 to 27.4)
Breastfeeding initiation time						
Breastfeeding initiation within 1 hour	1	1	1	1	1	–
Breastfeeding initiation after 1 hour	−56.2 (−94.9 to −17.4)	−39.9 (−90.3 to 10.6)	−40.5 (−60.1 to −20.9)		−42.5 (−61.1 to −23.9)	–
Child's gender						
Male babies	1	1	1			
Female babies	−53.1 (−104.7 to −1.6)	−52.9 (−103.0 to −2.9)	21.8 (−3.9 to 47.4)			
HIV disease stage						
HIV stage 1			1	1	1	1
HIV stage >1			−85.8 (−131.5 to −40.2)	−86.5 (−147.1 to −26.0)	−70.2 (−115.5 to −25.0)	−83.7 (−144.1 to −23.4)
Education						
Did not complete primary school			1		1	1
Completed primary school			29.2 (−8.6 to 67.1)		25.1 (−12.6 to 62.9)	24.4 (−12.9 to 61.6)
Secondary school and more			1.0 (−26.8 to 28.9)		−7.8 (−34.9 to 19.3)	−9.3 (−36.8 to 18.2)
Marital status						
Married/cohabiting mothers			1	1	1	1
Single mothers			−34.5 (−73.2 to 4.2)	−44.6 (−83.1 to −6.03)	−24.6 (−55.9 to 6.6)	−29.7 (−61.0 to 1.6)
Delivery						
Vaginal delivery			1	1		
C-section delivery			71.6 (11.7 to 131.4)	71.1 (11.1 to 131.2)		
Trial arm						
Lamivudine arm	1	1	1	1	1	1
Lopinavir/ritonavir arm	−33.4 (−69.2 to 2.3)	−65.3 (−116.4 to −14.1)	−12.8 (−31.6 to 6.1)	−12.9 (−38.2 to 12.4)	−15.8 (−32.6 to 1.0)	−19.2 (−41.9 to 3.6)

BMI, body mass index; EPBF, exclusive or predominant breast feeding.

load related to EPBF or any breast feeding. The same conclusion applied to these outcomes was combined in a composite endpoint representing HIV-1 disease progression. Unsurprisingly, mothers' baseline BMIs were consistently associated with an increase in the mothers' weight and CD4 cell count, and with a lower mean HIV-1 viral load for both EPBF and any breastfeeding groups.

In a review of the literature on weight change in the postpartum period, there appeared to be no association between breast feeding or generally between the mode

Table 2c Mothers' HIV-1 viral load change according to EPBF duration adjusted to different covariates: stratification presenting South Africa versus the other sites and pooled analysis

	South Africa		Burkina Faso, Uganda and Zambia		Pooled analysis	
	Unadjusted coefficient (95% CI)	Adjusted coefficient (95% CI)	Unadjusted coefficient (95% CI)	Adjusted coefficient (95% CI)	Unadjusted coefficient (95% CI)	Adjusted coefficient (95% CI)
Dependent variable=viral load (coefficient×10^3)						
EPBF duration (months)	4.5 (–3.4 to 12.4)	–3.6 (–11.5 to 4.4)	5.4 (–7.1 18.0)	2.0 (–11.3 15.4)	6.2 (–2.5 to 14.9)	1.7 (–7.3 to 10.8)
Baseline BMI (kg/m^2)	–7.7 (–10.9 to –4.6)	–14.5 (–17.9 to –11.0)	–4.7 (–8.5 to –1.0)	–5.7 (–9.8 to –1.6)	–6.5 (–9.2 to –3.8)	–8.0 (–11.0 to –4.9)
Mother's age (years)	–2.7 (–5.3 to –0.1)	–2.7 (–5.5 to 0.1)	–1.9 (–4.6 to 0.8)	–4.5 (–7.7 to –1.4)	–2.1 (–4.3 to 0.1)	–4.5 (–7.0 to –2.0)
Breastfeeding initiation time						
Breastfeeding initiation <1 hour	1	1				
Breastfeeding initiation >1 hour	70.5 (41.3 to 99.7)	45.1 (13.5 to 76.7)				
Child's gender						
Male babies	1	1	1	1	1	1
Female babies	–49.1 (–79.4 to 18.7)		–19.5 (–48.5 to 9.4)	–36.5 (–66.0 to 7.2)	–25.3 (–49.2 to –1.4)	–35.2 (–59.2 to –11.1)
Education						
Did not complete primary school			1	1	1	1
Completed primary school			–10.2 (–53.9 to 33.5)	2.9 (–41.4 to 47.2)	–5.0 (–45.1 to 35.2)	13.4 (–26.9 to 53.8)
Secondary school and more			–76.7 (–108.1 to –45.3)	–73.4 (–105.9 to –41.0)	–72.7 (–98.7 to –46.7)	–62.0 (–89.7 to –34.3)
Marital status						
Married/cohabiting mothers	1	1				
Single mothers	55.6 (21.6 to 89.5)	127.9 (92.8 163.0)				
Delivery						
Vaginal delivery	1	1	1	1	1	1
C-section delivery	118.5 (86.4 to 150.5)	143.2 (108.8 to 177.5)	72.6 (6.8 to 138.4)	84.2 (17.6 to150.7)	90.8 (49.8 to 131.8)	105.5 (65.2 to 145.7)
Parity						
Primipara	1	1	1	1	1	1
Multipara	66.5 (34.8 to 98.2)	125.9 (90.5 to 161.2)	47.7 (12.1 to 83.2)	56.7 (15.1 to 98.2)	54.8 (26.7 to 83.0)	65.1 (32.8 to 97.4)
Trial arm						
Lamivudine arm	1	1	1	1	1	1
Lopinavir/ritonavir arm	–48.4 (–77.6 to –19.2)	–37.6 (–67.5 to –7.6)	39.9 (12.4 to 67.4)	47.0 (17.9 to 76.1)	22.6 (–0.0 to 45.2)	31.1 (7.1 to 55.0)
Birth weight (g)	0.0 (0.0 to 0.1)	0.1 (0.0 to 0.1)	0.0 (0.0 to 0.1)	0.1 (0.0 to 0.1)		

BMI, body mass index; EPBF, exclusive or predominant breast feeding.

of infant feeding, and postpartum weight loss. However, C-section delivery was a risk factor for postpartum weight loss,[28] similar to our findings. South Africa had markedly lower rates of vaginal deliveries versus other countries (table 1b). In the year 2000, studies were published demonstrating that elective C-section before the labour and before the rupture of membranes added protection against HIV transmission to the newborn.[29 30] The lower rates of vaginal deliveries in South Africa were likely due to the country policies (influenced by the scientific

Table 2d Mothers' HIV-1 disease progression according to EPBF duration adjusted to different covariates: stratification presenting South Africa versus the other sites and pooled analysis

	South Africa		Burkina Faso, Uganda and Zambia		Pooled analysis	
	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
EPBF duration (months)	1.0 (0.9 to 1.1)		1.1 (1.0 1.2)	1.0 (0.9 to1.1)	1.1 (1.0 to 1.1)	1.1 (1.0 to 1.2)
Mother's age (years)			1.0 (1.0 to 1.1)	1.0 (1.0 to 1.1)		1.0 (1.0 to 1.0)
Child's gender						
Male babies			1		1	1
Female babies			0.8 (0.6 to 1.0)		0.8 (0.6 to 1.0)	0.8 (0.6 to 1.0)
HIV disease stage						
HIV stage 1			1	1		
HIV stage >1			4.0 (2.5 to 6.2)	4.2 (2.6 to 6.5)		
Marital status						
Married/cohabiting mothers			1	1	1	1
Single mothers			1.6 (1.1 to 2.2)	1.8 (1.3 to 2.6)	1.5 (1.2 to 1.9)	1.6 (1.3 to 2.1)
Trial arm						
Lamivudine arm			1	1	1	1
Lopinavir/ritonavir arm			1.3 (1.0 to 1.6)	1.3 (1.0 to 1.7)	1.3 (1.0 to 1.6)	1.3 (1.0 to 1.6)
Birth weight (g)			0.9 (0.8 to 1.0)			

EPBF, exclusive or predominant breast feeding.

evidence) that supported HIV-infected women towards delivering HIV-free babies. This support included free formulas and probably scheduled C-section for the HIV-infected pregnant women and mothers. Why the rest of the countries did not implement the same policy is certainly a matter of affordability and availability of local resources. Another reason is that C-section rate is 'recklessly high' in South Africa where up to 90% of pregnant women deliver through this method in private hospitals (The Guardian, https://www.theguardian.com/world/2014/sep/24/caesarean-section-south-africa (accessed on 27 October 2017)). This practice may have spilled over but at a lesser extent into public health facilities. We believe this practice has not skewed our results since these C-section deliveries were not medically indicated at first hand, at least not based on a vaginal delivery risk; therefore, they are not done on women with poorer health status. Actually, South African women had the lowest mean HIV-1 viral load and the highest mean BMI.

Yet, this review of literature[28] found that less educated mothers (<12 years of schooling) were at risk of postpartum weight retention; we found that higher educated women (secondary school or further) were at risk of that weight retention. This difference in our finding may be explained by the difference in our categorisation of the education variable. In our study, less educated participants included only women with primary school level, meaning around 6 years of schooling. Therefore, the results of the two studies are not really comparable. A higher education level was also a factor associated with a slower HIV-1 disease progression. This finding is consistent with our result that higher educated women retained more weight.

In a further review of literature on the effects of lactation on the mother's body weight, it is clear that the assumption that the postpartum weight loss is due to the high energy demand associated with lactation has been challenged by many studies.[31] Some reports conflict with our own findings, such as the one in KwaZulu Natal, where HIV-1-infected mothers at between 8 and 24 weeks had a mean weight loss of 1.4 kg in contrast to a 0.4 kg weight gain in HIV-1-uninfected mothers (P=0.01) during breast feeding.[15]

Regarding the change in CD4 cell count, the South African data support the conclusion that CD4 cell count did not differ significantly between women who breast fed and those who did not.[32] This finding contradicts the Kenyan study that found that the rate of CD4 cell count decline was higher in breastfeeding than in non-breastfeeding mothers.[13] However, in that Kenyan study, HIV-1 RNA levels did not differ significantly between breastfeeding and formula-feeding mothers.

Regarding HIV-1 disease progression, the same data showed no deleterious effect of breast feeding in HIV-1-infected mothers, similar to our study findings. The outcome variables were the CD4 and CD8 cell count, the mothers' illness and mortality, and their haemoglobin levels.[32] Another study from Malawi reached the

Table 3a Mothers' weight change according to any breastfeeding duration adjusted to different covariates: stratification presenting South Africa versus the other sites and pooled analysis

	South Africa		Burkina Faso, Uganda and Zambia		Pooled analysis	
	Unadjusted coefficient (95% CI)	Adjusted coefficient (95% CI)	Unadjusted coefficient (95% CI)	Adjusted coefficient (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
		Weight				
Any breastfeeding duration (months)	0.3 (–0.2 to 0.8)	–0.1 (–0.3 to 0.0)	–0.0 (–0.3 to 0.2)	0.1 (0.0 to 0.3)	–0.0 (–0.3 to 0.2)	–0.0 (–0.2 to 0.1)
Baseline BMI (kg/m^2)	2.5 (2.4 to 2.7)	2.5 (2.3 to 2.6)	2.5 (2.4 to 2.6)	2.4 (2.3 to 2.5)	2.5 (2.4 to 2.6)	2.4 (2.3 to 2.5)
Mothers' age (years)	0.8 (0.5 to 1.2)	0.2 (0.0 to 0.3)	0.5 (0.4 to 0.6)	0.1 (0.1 to 0.2)	0.5 (0.4 0.7)	0.1 (0.1 to 0.2)
HIV disease stage						
HIV stage 1	1	1	1			
HIV stage >1	12.4 (–4.5 to 29.4)	6.4 (0.0 to 12.7)	–2.8 (–6.4 to 0.8)			
Education						
Did not complete primary school			1	1	1	1
Completed primary school			3.9 (2.0 to 5.9)	0.3 (–0.6 to 1.1)	4.4 (2.2 to 6.5)	0.6 (–0.3 to 1.5)
Secondary school and further			2.7 (1.2 to 4.1)	0.9 (0.2 to 1.5)	3.1 (1.5 to 4.6)	1.0 (0.4 to 1.7)
Marital status						
Married/cohabiting mothers	1				1	
Single mothers	–3.1 (–7.2 to 0.9)				–1.2 (–3.0 to 0.5)	
Delivery						
Vaginal delivery			1		1	
C-section delivery	3.7 (–0.4 to 7.9)	–1.6 (–3.2 to 0.0)	4.5 (1.5 to 7.6)		4.4 (2.1 to 6.7)	–1.2 (–2.1 to –0.2)
Parity						
Primipara	1	1	1	1	1	
Multipara	6.1 (1.9 to 10.3)		3.1 (1.4 to 4.7)		3.9 (2.3 to 5.4)	
Trial arm						
Lamivudine arm	1	1	1	1	1	
Lopinavir/ritonavir arm	2.0 (–2.0 to 6.1)	0.7 (–0.8 to 2.2)	–0.1 (–1.4 to 1.3)	–0.3 (–0.9 to 0.3)	0.3 (–1.0 to 1.6)	0.1 (–0.7 to 0.4)

BMI, body mass index.

same conclusion that breast feeding was not associated with higher risk of maternal morbidity or mortality.[33] A study in Zambia concluded in the same direction that at 12 months after delivery, there was no difference in mortality between women who breast fed for a short duration (4 months) versus those who breast fed for a duration of their own choice.[17] An individual patient data meta-analysis on mortality among HIV-1-infected mothers according to children's feeding modality confirmed that the risk of dying within 18 months post partum was not significantly affected by the infants' feeding modality (ie, ever vs never breast fed).[34]

In healthy breastfeeding mothers, the postpartum weight loss would be around 0.5 kg per month among population with relatively high mean of BMI. The mechanism of the weight loss would be burning of 483–538 kcal per day.[35 36] Therefore, losing weight after birth is likely when the mother's calorie intake does not cover the calorie expense related to breast-milk production. Considering these findings, we think that energy

Table 3b Mothers' CD4 cell count change according to any breastfeeding duration adjusted to different covariates: stratification presenting South Africa versus the other sites and pooled analysis

	South Africa		Burkina Faso, Uganda and Zambia		Pooled analysis	
	Unadjusted coefficient (95% CI)	Adjusted coefficient (95% CI)	Unadjusted coefficient (95% CI)	Adjusted coefficient (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
		CD4 cell count				
Any breastfeeding duration (months)	0.4 (–6.8 to 7.6)	–2.4 (–9.5 to 4.7)	1.2 (–5.8 to 8.3)	9.8 (–2.1 to 21.8)	1.5 (–3.9 to 7.0)	5.7 (0.4 to 10.9)
Baseline BMI (kg/m^2)			4.9 (2.4 to 7.3)	5.7 (2.4 to 9.1)	3.3 (1.3 to 5.3)	4.2 (1.5 to 6.9)
Mother's age (years)	–3.1 (–7.5 to 1.2)		–4.9 (–7.3 to –2.5)	–6.5 (–8.9 to –4.1)	–4.7 (–6.9 to –2.6)	–6.2 (–8.4 to –4.1)
Haemoglobin concentration (g/dL)	33.3 (12.7 to 53.8)	33.9 (13.5 to 54.3)	15.2 (7.8 to 22.6)	15.7 (7.2 to 24.3)	19.3 (12.3 to 26.4)	16.7 (9.0 to 24.4)
Breastfeeding initiation time						
Within 1 hour			1		1	
After 1 hour	–56.2 (–94.9 to –17.4)		–40.5 (–60.1 to –20.9)		–42.5 (–61.1 to –23.9)	
Child's gender						
Male babies	1	1	1			
Female babies	–53.1 (–104.7 to –1.6)	–54.1 (–104.3 to –3.6)	21.7 (–3.9 to 47.4)			
HIV stage						
HIV stage 1			1	1	1	1
HIV stage >1			–85.8 (–131.5 to –40.2)	–91.5 (–152.9 to –30.1)	–70.2 (–115.5 to –25.0)	–88.8 (–148.3 to –29.3)
Education						
Did not complete primary school			1		1	1
Completed primary school			29.2 (–8.6 to 67.1)		25.1 (–12.6 to 62.9)	19.9 (–16.7 to 56.5)
Secondary school and further			1.0 (–26.8 to 28.9)		–7.8 (–34.9 to 19.3)	–17.4 (–43.7 to 9.5)
Marital status						
Married/cohabiting mothers			1	1	1	1
Single mothers			–34.5 (–73.2 to 4.2)	–43.1 (–81.5 to –4.6)	–24.6 (–55.9 to 6.6)	–43.3 (–72.8 to –13.7)
Delivery						
Vaginal delivery			1	1		
C-section delivery			71.6 (11.7 to 131.4)	71.8 (11.9 to 131.7)		
Parity						
Primipara			1			
Multipara						
Trial arm						
Lamivudine arm	1	1	1	1	1	1
Lopinavir/ritonavir arm	–33.4 (–69 to 2.3)	–58.7 (–109.6 to –7.8)	–12.8 (–31.6 to 6.1)	–13.4 (–38.6 to 11.8)	–15.8 (–32.6 to 1.0)	–19.2 (–41.9 to 3.6)

BMI, body mass index.

requirement and thus the metabolic stress related to breast feeding would be quite bearable. This may explain why in our study HIV-1-infected, immune-competent and breastfeeding mothers' health status was not deteriorated by breast feeding. This evidence inspires the idea that option A peri-exposure antiretroviral prophylaxis might still have pertinent indications since breast feeding remained the most frequent feeding

Table 3c Mothers' HIV-1 viral load change according to any breastfeeding duration adjusted to different covariates: stratification presenting South Africa versus the other sites and pooled analysis

	South Africa		Burkina Faso, Uganda and Zambia		Pooled analysis	
	Unadjusted coefficient (95% CI)	Adjusted coefficient (95% CI)	Unadjusted coefficient (95% CI)	Adjusted coefficient (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
		HIV-1 viral load (coefficient×10^3) copies/µL				
Any breastfeeding duration (months)	11.2 (6.8 to 15.6)	7.7 (3.4 to 12.1)	5.9 (–1.5 to 13.2)	2.5 (–5.2 to 10.2)	9.8 (4.9 to 14.7)	6.1 (1.0 to 11.2)
Baseline BMI (kg/m^2)	–7.7 (–10.9 to –4.6)	–14.0 (–17.4 to –10.6)	–4.7 (–8.5 to –1.0)	–5.7 (–9.8 to –1.5)	–6.5 (–9.2 to –3.8)	–7.6 (–10.7 to –4.5)
Mother's age (years)	–2.7 (–5.3 to –0.1)	–3.4 (–6.2 to –0.6)	–1.9 (–4.6 to 0.8)	–4.6 (–7.8 to –1.4)	–2.1 (–4.3 to 0.1)	–4.8 (–7.3 to –2.3)
Breastfeeding initiation time						
Within 1 hour	1	1				
After 1 hour	70.5 (41.3 to 99.7)	34.2 (2.7 to 65.7)				
Child's gender						
Male babies	1		1	1	1	1
Female babies	–49.1 (–79.4 to –18.7)		–19.5 (–48.5 to 9.4)	–37.2 (–66.6 to –7.9)	–25.3 (–49.2 to –1.4)	–36.2 (–60.2 to –12.2)
Education						
Did not complete primary school			1	1	1	1
Completed primary school			–10.2 (–53.9 to 33.5)	4.7 (–39.8 to 49.3)	–4.9 (–45.1 to 35.2)	16.6 (–23.8 to 57.0)
Secondary school and further			–76.7 (–108.1 to –45.3)	–70.7 (–104.4 to –37.1)	–72.7 (–98.7 to –46.7)	–54.5 (–82.8 to –26.1)
Marital status						
Married/cohabiting mothers	1	1			1	
Single mothers	55.6 (21.6 to 89.5)	124.9 (89.9 to 160.0)				
Delivery						
Vaginal delivery	1	1	1	1	1	1
C-section delivery	118.5 (86.4 to 150.5)	137.0 (102.7 to 171.2)	72.6 (6.8 to 138.4)	84.4 (18.0 to 150.7)	90.8 (49.8 to 131.8)	104.7 (64.5 to 144.9)
Parity						
Primipara	1	1	1	1	1	1
Multipara	66.5 (34.8 to 98.3)	125.0 (89.8 to 160.3)	47.7 (12.1 to 83.2)	57.2 (15.6 to 98.8)	54.8 (26.7 to 83.0)	65.0 (32.7 to 97.3)
Trial arm						
Lamivudine arm	1	1	1	1	1	1
Lopinavir/ritonavir arm	–48.4 (–77.6 to –19.2)	–35.0 (–64.8 to –5.3)	39.9 (12.4 to 67.4)	47.6 (18.6 to 76.7)	22.6 (–60.2 to 45.2)	31.9 (8.0 to 55.8)

BMI, body mass index.

option in sub-Saharan Africa and since breast milk might still host HIV-1 reservoirs that mothers' prophylaxis could not always 100% suppress.[37]

Strengths and limitations

Our study has been implemented in four countries in Africa, including Burkina Faso (West), South Africa and Zambia (South) and Uganda (East). Therefore, we consider our study population representative of the sub-Sahara African population. The data were also collected in the rigorous context of a clinical trial, which minimised the loss to follow-up, the missing data as well as other data collection errors, and therefore improved the quality of our data.

However, the selection associated with the environment of a clinical trial—usually quite different from a routine environment—may have biased our findings. Nonetheless, our endpoints (mother's weight, CD4 cell count and HIV-1 viral load) were sufficiently robust for us to vouch for their validity. Another point of note is the stratification of the participants into two strata, that is, South Africa versus Burkina Faso, Uganda and Zambia. This stratification reduced the sample size in South Africa. Thus, some

Table 3d Mothers' HIV-1 disease progression according to any breastfeeding duration adjusted to different covariates: stratification presenting South Africa versus the other sites and pooled analysis

	South Africa		Burkina Faso, Uganda and Zambia		Pooled analysis	
	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
		HIV disease progress				
Any breastfeeding duration (months)			1.1 (1.0 to 1.2)	1.0 (0.9 to 1.1)	1.0 (0.9 to 1.0)	1.0 (0.9 to 1.0)
Baseline BMI (kg/m^2)			1.0 (1.0 to 1.1)			
Mother's age (years)				1.0 (1.0 to 1.1)	1.0 (0.9 to 1.0)	
Breastfeeding initiation time						
Within 1 hour	1					
After 1 hour						
Child's gender						
Male babies			1		1	
Female babies			0.8 (0.6 to 1.0)		0.8 (0.6 to 1.0)	
HIV stage						
HIV stage 1			1	1	1	1
HIV stage >1			4.0 (2.5 to 6.2)	4.2 (2.6 to 6.6)	4.4 (2.8 to 6.7)	4.6 (2.9 to 7.3)
Education						
Did not complete primary school			1			1
Completed primary school						1.4 (0.9 to 2.0)
Secondary school and further						0.7 (0.5 to 0.9)
Marital status						
Married/cohabiting mothers			1	1		
Single mothers			1.6 (1.1 to 2.2)	1.8 (1.2 to 2.6)	1.5 (1.2 to 1.9)	
Trial arm						
Lamivudine arm			1	1	1	1
Lopinavir/ritonavir arm			1.3 (1.0 to 1.6)	1.3 (1.0 to 1.7)	1.3 (1.0 to 1.6)	1.3 (1.0 to 1.6)

BMI, body mass index.

of the modelling for South Africa could be less rigorous, and the findings regarding the risk factors there may not truly reflect the reality.

CONCLUSION

Breast feeding, whatever the type (exclusive or any) as far as this study can conclude, was not a risk factor for the HIV-1-infected mothers' weight, CD4 cell count and HIV-1 viral load change, or HIV-1 disease progression, keeping in mind that all the participants had a baseline CD4 cell count >350 cells/µL. The mothers' baseline high weight and high haemoglobin concentration were important factors in being consistently associated with an improvement of the outcome variables at stake. A higher education level was also a factor associated with a slower HIV-1 disease progression. Considering the benefits of breast milk for infants, and the consensus results from different studies elsewhere that breast feeding does not harm HIV-1-infected mothers, this study also supports the WHO 2016 guidelines on infant feeding, which indicate that mothers living with HIV should breast feed for at least 12 months and up to 24 months, provided that the right treatment or prophylaxis for the infection is given where formula feeding is unsafe.[12]

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