Acceptability of formula-feeding to prevent HIV postnatal transmission, Abidjan, Côte d'Ivoire: ANRS 1201/1202 Ditrame Plus Study.

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Acceptability of formula-feeding to prevent HIV postnatal transmission, Abidjan, Côte d'Ivoire, 01-04: ANRS 1201/1202 Ditrame-Plus Study

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Running head: Acceptability of formula feeding in Africa

Abstract

Objective: To describe the maternal acceptability of formula-feeding proposed to reduce postnatal HIV transmission in Abidjan, Côte d'Ivoire.

Methods: Each consenting HIV-infected pregnant women, age≥18 years, who received a perinatal antiretroviral prophylaxis was eligible. Two hierarchical infant-feeding options were proposed antenatally: exclusive formula-feeding or short exclusive breastfeeding. Formula-feeding was provided free up to age nine months. Determinants of acceptability were analyzed using a logistic regression.

Results: Between March 2001 and March 2003, 580 women delivered: 97% expressed their infant-feeding choice before delivery; 53% chose formula-feeding. Significant prenatal determinants for refusing formula-feeding were: living with her partner, being Muslim, having a low educational level, being followed in one of the study sites, having not disclosed her HIV-status and having been included within the first six months of the project. Among the 295 mothers who formula-fed, the Kaplan-Meier probability of success of the formula-feeding option was 93.6% at Day2 (95% CI: 90.7%-96.3%) and 84.2% at 12 months (95% CI: 79.9%-88.5%): 46/295 (15.6%) women breastfed at least once, of whom 41% mixed-breastfed temporarily at Day2 because of social stigma or newborn poor health.

Conclusions: Formula-feeding was better accepted than anticipated. This social acceptability needs to be balanced with mother-child long-term health outcomes to guide safe recommendations on infant-feeding among HIV-infected women in African urban settings with access to tap water.

Keywords: Africa; HIV infections; Mother-to-Child transmission; formula-feeding; behavioural research; acceptability; cohort study.

Introduction

Every day, 1900 children acquire human immunodeficiency virus type 1 (HIV) infection from their mother during the pregnancy, the delivery or postnatally in Africa [1]. Since 1998, different short course antiretroviral interventions have proven their efficacy in preventing peri-partum mother-to-child transmission (PMTCT) of HIV [1, 2]. However, postnatal transmission (PT) of HIV through breast-milk remains of great concern in Africa where breastfeeding is a common practice with the longer the duration of breastfeeding, the higher the risk of PT [3, 4]. Moreover, this subsequent PT risk reduced the long-term overall efficacy of peri-partum antiretroviral regimens at age two years [4]. A Kenyan randomized trial comparing breastfeeding to formula-feeding in the absence of any use of antiretroviral therapy showed an additional PT risk of 16% at age two years [5]. Most breast-milk transmission occurred early, with 75% of the risk difference between the two arms occurring by six months [5]. The overall risk of PT was estimated to be 8.9 new cases per 100 child-years of breast-feeding (95% confidence interval [CI], 7.8–10.2) in a recent pooled analysis [6].

Peri-partum antiretroviral interventions aimed to PMTCT should be rapidly implemented on a large-scale-basis to control the paediatric epidemic in Africa [7]. In such a context, it is also urgent to evaluate safe interventions to reduce PT of HIV and maximize the effect of perinatal interventions. Among them, alternatives to prolonged breastfeeding such as formula-feeding could constitute an option in African settings where clean water is widely available [8]. In the selected setting of the randomized Kenyan trial, formula-feeding prevented 44% of MTCT infections and was associated with significantly improved HIV-1-free survival compared to breastfeeding [5]. However, the social acceptability and whether breast-milk PT risk exceeds or not the potential risk of formula-associated mortality remains unknown and needs to be assessed in a more generalizable population. Indeed, the social acceptability of such a public health intervention representing a real risk of stigmatization is a key issue in assessing its field

effectiveness. This information is needed in the scaling-up process of PMTCT programs in Africa [7].

The ANRS 1201/1202 Ditrame-Plus program conducted in Abidjan, Côte d'Ivoire from 2001 to 2005 aimed at evaluating the field effectiveness of a package of interventions targeted on HIV-infected pregnant women and their children to prevent MTCT and its consequences [9, 10]. In this specific urban setting, guarantying a generalized access to municipal water of good quality [11], our program included a post-partum component with a systematic proposal of alternatives to prolonged breastfeeding.

The objective of the present study is to describe the uptake of formula-feeding from birth as an alternative to prolonged and predominant breastfeeding in HIV-infected women followed over two years in the Ditrame-Plus program.

Methods

Study sites

The ANRS 1201/1202 Ditrame-Plus project was conducted in the two most densely populated districts of Abidjan, Côte d'Ivoire. We selected the Yopougon University Hospital and six community-run health facilities to set up HIV counselling and testing services within the antenatal clinics. Two of them were upgraded to serve as study clinics for inclusion and follow-up of mother-child pairs. HIV seroprevalence estimates in pregnant women have consistently been in the range of 11-12% in these parts of Abidjan during the study period [12, 13].

Study design

The study design was a non randomized open-label prospective cohort with a peri-partum antiretroviral intervention (ZDV + NVP or ZDV+3TC+NVP) [9] then a post-partum

intervention focusing on both infant-feeding and the case management of HIV-infected children.

Inclusion procedures

Between March 6th 2001 and March 6th 2003, all consenting pregnant women attending the selected prenatal clinics, living within the city limits, presenting at< 36 weeks of gestation and aged at least 18 years were tested for HIV infection [9, 14]. HIV infection was defined by two sequential positive rapids tests (Determine ®, Abbot Laboratories, Abbot Park, IL, USA and Genie II ®, Bio-Rad**,** Marnes-La-Coquette, France) performed onsite later confirmed using Enzyme-Linked Immunosorbent Assays [15]. Post-test counselling and announcement of the seropositive status were made if both test results were positive. HIV-infected women (HIV-1 or dually reactive HIV-1+2) were systematically eligible for the program if hemoglobinemia was ≥7 g/deciliter (dl).

Study interventions

Those women who fulfilled all the above inclusion criteria, accepted the study principles and signed an informed consent were included from 32 weeks of gestation and received a peripartum antiretroviral intervention as follows [9]: oral ZDV (600mg) or ZDV (600mg) + 3TC (300mg) daily up to delivery and a single NVP tablet (200 mg) at beginning of labour. Intra-partum treatment was self-administrated by the woman as soon as the labour had started. The ZDV+3TC maternal regimen was continued for three days post-partum. The child received a neonatal prophylaxis: a single dose of NVP (2 mg/Kg on Day 2 directly observed) and a seven-day course of ZDV (syrup 2 mg/ kg every 6 hours).

Women received a supplementation in multivitamins [16], iron and folates, and malaria chemoprophylaxis according to Ivorian guidelines.

At inclusion, pregnant women were individually counselled about the advantages of breast-milk and the risk of PT during 30 minutes. They were systematically and hierarchically

proposed two alternatives to prolonged breastfeeding: exclusive formula-feeding from birth or exclusive breastfeeding with early cessation within the fourth month. The advantages of these interventions, i.e. the reduction of the risk of HIV transmission through breast-milk, and their disadvantages, i.e. the possible stigmatization and the potential risks for infant health, were fully discussed during the subsequent weekly prenatal visits until delivery.

The first option, formula-feeding from birth, was proposed free of charge up to nine months of age and facilitated by the use of a single oral dose of cabergoline for inhibiting lactation [17]. The second option proposed, the practice of a short exclusive breastfeeding period followed by early weaning to obtain complete cessation of breastfeeding between three and four months of age, was further described elsewhere [10]. All women could express their feeding choice until birth and the staff supported their choice and counselled them accordingly. The following material was provided free of charge to women willing to refrain from breastfeeding: bottles, teats, bottles brush, pan to sterilize, thermos to keep safely clean water, and a controlled distribution of local powdered infant formula (one box at each follow-up visit) until nine months of age. These women were also trained to prepare and store correctly and hygienically bottles, and to feed in nutritionally adequate quantities their child, with clean hands and using clean utensils [18]. Cup-feeding was encouraged after three month of age. Material was delivered prenatally when the choice was expressed.

At the beginning of the project, daily life in Abidjan was compatible with the use of a locally available formula-milk that we chose to reduce stigmatisation.

A systematic vitamin A supplementation was provided to children according to WHO recommendations. A systematic contraception, including condoms was also proposed to women according to their feeding choice and will be described elsewhere.

Follow-up procedures

Two clinics were exclusively dedicated to the follow-up of the 800 mother-infant pairs, with 60 health care workers recruited from the local area specifically trained for this program. Care services dispensed were also available whenever needed between scheduled visits. All transport costs were reimbursed and all care expenses related to any scheduled visit or clinical event were entirely supported by the project.

Pregnant women were followed weekly until delivery and mother-infant pairs were seen 48 hours after birth, weekly until six weeks of age, monthly until nine months of age, and every three months until their second birthday. At each scheduled visit, clinical, nutritional, psychosocial and biological follow-up of both mothers and infants was proposed.

Four nutritionists individually counselled the women about infant-feeding practices whenever needed. Collective sessions were frequently organized to explain to non breastfeeding mothers how to safely prepare artificial feeding, use appropriate complementary feeding or cook the baby food. If a woman had declared her intent to formula-feed her child and had received the formula-feeding material but thereafter decided to implement breastfeeding for any reason, the material was picked-up again to avoid mixed feeding practices or a spill-over effect. To identify possible undeclared breastfeeding practices to the team among women who chose to formula-feed, medical examination of mother's breast was performed to look for breast-milk discharge at each scheduled visit, and the child was snuggled-up in her/his mother arms to observe her/his suckling behaviour during the interview. A maternal blood sample was taken at Day 2 in women who declared to formula-feed to measure the blood prolactinemia: we used this biological indicator as a proxy of the compliance to formula-feeding, low values (<40ng/ml) being expected in those women who had taken cabergoline after delivery and not breastfed.

Paediatric blood samples were taken for paediatric HIV diagnosis at Day 2, week 4-6, then three monthly until one year, month 18 and 24 and two months after complete cessation of

breastfeeding for those breastfed. Paediatric HIV infection case was initially diagnosed using a commercial plasma HIV-1 RNA assay (Versant bDNA HIV RNA kit version 3.0, Bayer diagnostics, Emeryville, CA, USA). [19]. From 2003, a TaqMan HIV-1 RNA real-time PCR test was used for this purpose [20]. HIV-infected children received a cotrimoxazole prophylaxis (25 mg/kg per day) systematically from six weeks of age until at least their first birthday.

The study protocol was approved by the Ethical Committee of the National AIDS Control Programme in Côte d'Ivoire and the Institutional Review Board of the French Agence Nationale de Recherches sur le SIDA (ANRS), the primary sponsor.

In March 2003, because of the political troubles in Côte d'Ivoire, we decided to stop to propose the formula-milk option, considering the risks of breakdown distribution and loss to follow-up was becoming unacceptable and we proposed to every woman the exclusive breastfeeding option combined to early weaning up to the end of the project.

Data collection

At each scheduled visit, clinical events that occurred in both mothers and children since the last visit were documented and infant-feeding practices were recorded via structured questionnaires by trained social workers who were not involved in nutritional counselling. Women were asked if their child had been given breast-milk, artificial milk or both since the last visit. Fluids and foods other than any milk were documented using a 24-hour and a seven-day recall history. Social workers went over a detailed list of 15 commonly used fluids or foods. Women were asked if these fluids, foods or some other items not listed had been given in the previous seven days, and if so in what amount (24 hour recall history) and how frequently in the past seven days. The first liquid given after birth was recorded at the Day2 visit.

Infants were classified at each scheduled visit as breastfed, mixed fed or artificial fed using these recall histories [21]. We used the following WHO definitions to allow a better comparability of results between studies [22, 23]: *Exclusive breastfeeding* means giving a child no other food or drink, including no water, in addition to breastfeeding with the exception of medicines, vitamin drops or syrups, and mineral supplements; *Predominant breastfeeding* means breastfeeding a child but also giving small amounts of water or water based drinks; *Artificial feeding* means feeding a child on artificial foods (including infant formula and powdered animal milk), and not breastfeeding at all. *Mixed feeding* means breastfeeding while giving non-human milk such as infant formula or food-based fluid, or solid food.

Statistical analysis

Among all HIV-infected pregnant women enrolled, we described the maternal infant-feeding choice formulated antenatally if any, then the feeding option implemented at Day 2 after delivery. Results were expressed in percentages with their 95% Confidence Interval (CI). Determinants for prenatal refusal of the formula-feeding option were explored using a logistic regression with the following variables: maternal age, parity, gestational age, living with a partner, with her mother-in-law, being a co-spouse, educational level, personal income, access to clean piped water, ethnic group, religion, maternal WHO clinical staging at entry, maternal CD4 cell count and viral load at entry. A stepwise descendant multivariate analysis included all variables with $p<0.25$ in the univariate analysis.

Women whose live-born infants were formula-fed at least once at Day 2 were classified to contribute to the formula-fed group whatever their prenatal choice. For mothers who decided to implement the formula-feeding option, we described the behavioural compliance to their infant-feeding choice practiced for the live-born children feed at least once. The Kaplan-Meier probabilities of formula-feeding success at given ages were computed until 12 months.

Formula-feeding failure was defined as having breastfed at least once, based on one of the following criteria: reporting of any breastfeeding from feeding recall histories or maternal breast-milk discharge, or child breastfeeding behaviour during visit. Determinants for failure of the formula-feeding option were explored using a multivariate logistic regression including the variables associated with the prenatal choice and the prenatal choice itself. Reasons for feeding switches over time were described. All statistical analyses were carried out with the SAS software (version 8.2; SAS Institute, Inc, Cary, NC, USA).

Results

Prenatal choice of infant-feeding option

From March 6th 2001 to March 6th 2003, 643 HIV-infected pregnant women were consecutively enrolled in the cohort (Figure 1). Nineteen women with HIV-2 infection only and 44 lost-to-follow-up prior to delivery were excluded from the analysis. Among the 580 pregnant women who delivered, 309 (53%) had expressed their willingness to formula-feed, 256 (44%) had planned to breastfeed and only 15 (3%) had not expressed any choice before delivery. The prenatal acceptability of formula-feeding was thus estimated to be 53% (95%CI: 49%-57%). Women who expressed their infant-feeding choice before delivery had a significant longer median duration of prenatal follow-up than those who did not formulate their choice before delivery: 34 days versus 16 days, respectively (Wilcoxon test, p=0.01). Women who expressed their choice before delivery had a similar median duration of prenatal follow-up according to their option chosen: 34 days in the formula-feeding group and 35 days among those who chose breastfeeding (Wilcoxon test, p=0.67). Overall, 93 women out of the 580 (16%) declared having hesitation in making their infant-feeding choice at the time of inclusion. The main reasons of hesitation for choosing the formula-feeding option reported by 88 women were as follows: fear from their partner reaction (39%), fear from their family circle reaction (31%), constraints of organization (13%), fear for their infant health (7%), logistic constraints (2%), and other reason (8%). Among these 88 uncertain women, 8% did not express any choice before delivery, 41% decided to formula-feed and 51% to breastfeed before delivery.

Prenatal determinants for refusing formula-feeding

Among the 565 pregnant women who expressed a prenatal choice (Table 1), living with her partner, being foreigner, or native from the North Mande or Gur ethnic groups, being Muslim, having a low educational level, living in a shared housing, having no access to tap water,

being followed in the clinic based in Abobo district, having not shared her HIV status with someone else were significantly associated with refusal of the formula-feeding option in a univariate logistic regression analysis (Table 1). Neither maternal clinical stage nor CD4 cell count) were associated with the prenatal choice (Table 1). In a multivariate adjusted analysis, a few socio-demographic variables remained significantly associated with the maternal refusal of the formula-feeding option (Table 2): living with her partner, being Muslim, having a low educational level, being followed in the Abobo centre, having not shared her HIV status with someone else and having been included in the project before September 2001 (in the first six-month period of the project). There was no longer significant association with the type of access to water.

There was a significant centre effect on the acceptability of formula-feeding, even adjusted on the other socio-demographic variables. In Abobo, there was a significant evolution of the refusal rate of formula-feeding over time, ranging from 34% in the March-August 2001 period, 51% in the September 2001-February 2002 period, 52% in the March-August 2002 period, up to 63% during the September 2002-March 2003 period (Chi-square for trend, p=0.0008). While in Yopougon, the refusal rate was lower and did not vary over time (p=0.45). When pooling the two centres, the time varying effect was no longer significant (p=0.078). The study site was a confounding factor in the analysis of the evolution of acceptability over time.

Neonatal implementation of infant-feeding option according to prenatal choice

Among the 309 mothers who had chosen formula-feeding prenatally, one woman was lost-to-follow-up after birth and 13 women could not implement any infant-feeding choice because their child died before their first feed (4%) and were excluded from the analysis of postnatal acceptability (Figure 1). At Day 2, 267 out of the 295 women (91%) who had chosen formula-feeding before birth had actually initiated this practice after birth in

agreement with their prenatal choice, and 28 (9%) changed their mind and decided to breastfed from birth (Figure 1). At Day 2, among those 267 who formula-fed consistently with their prenatal choice, 93% were exclusively formula-feeding while 7% initiated mixed-feeding temporarily from birth. Among those 19 uncertain women at birth, 11 (58%) finally succeed in implementing a definitely exclusive formula-feeding practice from Day 8, 5 (26%) decided to switch for the exclusive breastfeeding option and recurrent practice of mixed feeding were reported in 3 children (16%).

Among the 557 mothers whose live-birth was fed at least once, 295 (53%) initiated formula-feeding (267 women who had chosen formula-feeding prenatally + 22 women who had chosen exclusive breastfeeding prenatally + 6 who had not express their prenatal choice) and constituted the formula-feeding group for the present analysis (figure 1). Postnatal acceptability of the EBF option and its determinants were described elsewhere [10].

The baseline maternal socio-demographic, clinical, biological and delivery characteristics of the 295 women of the formula-feeding group are shown in Table 3. Overall, 63% lived with their partner, 33% with their family in law, 19% had a co-spouse, 25% were illiterate and half of them shared their HIV status with someone else. All but three had electricity at home, 59% lived in a collective housing, and everybody had access to tap water with 38% who had an individual access. Three-quarters of the women included were at WHO clinical stage 1 or 2. Their baseline median CD4 count was 386/cell mm^3 (IQR, 239-583) and their median plasma viral load was 4.3 log10 (IQR: 3.6-4.9). After delivery, 6% had a multiple birth, 6% a C-section, and 14% a low birth-weight newborn.

Postnatal acceptability of infant-feeding

In the formula-feeding group, from birth up-to 12 months, 46 (15.6%) women failed to maintain exclusive formula-feeding and breastfed at least once. The Kaplan-Meier probabilities of success of the formula-feeding practice were 93.6% at Day 2 (95% CI:

90.7%-96.5%); 86.7% at one month (95% CI: 82.7%-90.7%) and 84.2% at 12 months (95% CI: 79.9%-88.5%). Failures occurred before the 10th day in median (range: birth-319 days). Overall, 85% of failures occurred in the neonatal period and most of them at Day 2: 19 women (41%) mixed breastfed for the following reasons: forgot their formula-feeding material at delivery in maternity (n=6), family pressure (n=5), baby cry (n=4), midwives advice (n=3), unknown (n=1). Beyond the early neonatal period, the reasons for switching to breastfeeding were as follows: probable family pressure not admitted (n=12), family pressure admitted (n=10), logistic constraints (n=2), desire to breastfed (n=2). One child had not been breastfed by his mother but was considered as a failure since he had been breastfed by his aunt of which HIV status was unknown.

Determinants for formula-feeding failure after birth

In univariate analysis, none of the baseline prenatal variables was significantly associated with the subsequent failure of formula-feeding, but having a multiple birth or a low birth-weight newborn were significantly associated (Table 3). In an adjusted multivariate analysis, the only variables explaining the failure of formula-feeding were having a low birth-weight newborn: adjusted Odds Ratio (aOR: 2.4, 95% CI: 1.1-5.4), and a multiple birth (aOR: 2.0, 95% CI: 0.7-6.1).

Prolactin blood level as a biological marker as of compliance

Among the 267 women who received it before delivery, 263 women declared they had taken cabergoline after birth and had a blood sample taken for prolactin measurement at their first visit. Of these, 191 (73%) were precisely collected after Day 2, the other ones having been collected before. Of the 158 mothers who succeeded in formula-feeding and had a blood sample available for prolactin measurement, 87% had a low prolactin level (<40ng/l) from Day 2, which was consistent with their compliance to this option. Of the 32 women who

failed in practicing exclusive formula-feeding and had a prolactin measurement, 62% had a low prolactin level at Day 2 ($p=0.0009$).

Discussion

The Ditrame-Plus project being an open-label cohort, proposed systematically and hierarchically during the prenatal period two alternatives to prolonged breastfeeding to reduce mother-to-child transmission of HIV. By giving to HIV-infected pregnant women an informed choice and counselling and offering them all the equipment and formula free of charge to implement properly this option at birth, we were able to pragmatically capture its social acceptability and determinants, excluding the economical constraint reported to be one major limitation in low-income countries [23].

We deduct from our findings that the uptake of formula-feeding was high in this population usually practising prolonged breastfeeding [24, 25]. Almost all HIV-infected women expressed their infant-feeding choice before delivery. The formula-feeding option was better accepted than anticipated, greater than 50% in the prenatal period. Women living with their partner, illiterate, of Muslim religion, having not disclosed their HIV-status and included within the first six-month after the implementation of the project were more likely to refuse the formula-feeding option before delivery. For pregnant women who chose formula-feeding, the postnatal compliance to their prenatal choice was also high, more than 90%. Most failures occurred early in the early neonatal period (85%) and were mainly related to stigma (partner, familial or health-worker environment) or newborn health concerns (low birth-weight). Very few newborn were exposed to mixed-feeding after birth in this population, 6% within the first week of life and for a very short period of time.

Our cohort was conducted among HIV-infected pregnant women attending the community-run health facilities of two poor districts: a quite representative population of all social categories in Abidjan [10, 25]. Our findings could be extrapolated to the same unselected population. This cohort also provided prospective carefully collected data on infant feeding

practices from birth until 12 months of age. Standardized questionnaires were used to perform recall histories administered by trained health care workers other than those who counselled the women on infant feeding practices. As the interval between two visits was one week over the first two months then one month up-to nine months, then three months, we believe we provide an unbiased overview of the infant-feeding practices. In addition, by crossing information between the declared infant-feeding practices with the maternal breast examination and the child behaviour with her breast during the maternal interview at each clinical visit, we were able to detect quite correctly and early the mixed-feeding practices not recommended by the project. Finally, although not strictly sensitive, the high proportion of low blood prolactin level reaching 87% in formula-feeders was also consistent with the compliance to the non-breastfeeding option.

Several arguments justified our methodological choices in proposing the formula feeding option in this African urban setting. First, we proposed a cohort study design instead of a randomized clinical trial with a random allocation of the infant feeding group to minimize ethical considerations and the risk of non compliance inducing at-risk mixed feeding-practices already reported in the Kenya trial [5, 26]. Second, in Abidjan, municipal water of good quality was widely available but water storage was a common practice in most household, which might contribute to the contamination of drinking water [11]. This fact justifies, both the need for a timely counselling of pregnant women as early as possible before delivery to demonstrate them how to safely prepare formula feeding, and also the furniture of the material needed to prepare bottles and to store the boiled water. Third, we decided to provide formula-feeding free of charge to avoid practices of mixed-feeding in women who would like not to breastfed but with too limited resources to practice it correctly. As a result, the proportion of mixed feeding remained very low. Indeed, in others projects where formula-feeding was not

provided for free, the proportion of mixed feeding practices reached 30% among those who opted not to breastfed, mainly because of low socioeconomic status [27]. Fourth, we accepted to provide the breast-milk substitutes until nine months of age only to limit the introduction of such substitutes in older children commonly fed using the "family plate" and thus limit any potential spill-over effect of formula-feeding practice on close relatives children.

Overall, our study provides useful knowledge underlining that alternatives to breastfeeding are indeed acceptable and feasible in this West African urban population with access to tap water. In East Africa, Magoni et al. reported a 40% neonatal acceptance rate of formula-feeding offered free of charge in 306 mothers enrolled in a PMTCT program in an urban hospital centre in Kampala, Uganda [28]. Failure to maintain exclusive formula feeding was reported in 11% of the women up to 6 months of age, and consistent with our findings. These two studies argue in favour of providing formula-feeding free of charge in eligible women who opt for this option.

Our findings show that women who refused the formula-feeding option prenatally or failed to maintain exclusive formula-feeding up-to-12 months were under the social pressure of the family of the partner influencing the decision process about infant feeding practices. The fear of stigma could also explain the association reported between this prenatal refusal and the lack of prenatal disclosure of the woman HIV-status. These social factors must be carefully taken into account when counselling mothers on infant feeding options, with a clear emphasis on issues regarding confidentiality [29]. Finally, we interpret the association between the Abobo centre negative effect in choosing formula-feeding and the negative effect of being included during the initial phase of the project as the lack of self-confidence of their health care workers during the initial phase of the project. These difficulties in proposing alternatives to prolonged breastfeeding were already reported by the Ditrame-Plus team [30] and reflect the

man-power related field difficulties that may be encountered, even with an appropriate intervention.

These findings lead to formulate several practical recommendations. First, there is a need for an adequate counselling and training of health care workers on infant-feeding counselling, including the involvement of midwives in delivery room to avoid mixed feeding practices in HIV-infected women who opt for formula-feeding [30]. One should bear in mind that health care workers have a key role to play in reaching successful practices of alternatives to prolonged breastfeeding, even if this counselling remains difficult to standardize. Second, there is an urgent need to find innovative approaches to involve positively fathers and partners in PMTCT programs so that the communication within couples could be improved and the infant-feeding choice facilitated as soon as before delivery. Third, reducing overall stigmatization of people living with HIV/AIDS should be useful in helping HIV-infected pregnant women regarding their infant-feeding choice and practice. Finally, it should be also acknowledged that women of low socioeconomic status who opt not to breastfeed require support to avoid compromising the nutritional status of infants [27]. In other words, providing breast-milk substitutes and equipment needed for free to HIV-infected women who want opt for this option and in settings where this practice could be safely conducted should be a strategic public health decision, as important as the universal access to antiretroviral interventions to reduce MTCT [31].

This social acceptability needs to be balanced with mother-child long-term health outcomes measured at age two years, accounting for PT, morbidity and mortality events in children in order to guide safe recommendations on alternatives to breastfeeding among HIV-infected women in African cities such as Abidjan.

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APPENDIX

Composition of the ANRS 1201/1202 Ditrame-Plus Study Group

Principal Investigators: François Dabis, Valériane Leroy, Marguerite Timite-Konan, Christiane Welffens-Ekra. Coordination in Abidjan: Laurence Bequet, Didier K. Ekouévi, Besigin Tonwe-Gold, Ida Viho. Methodology, biostatistics and data management: Gérard Allou, Renaud Becquet, Katia Castetbon, Laurence Dequae-Merchadou, Charlotte Sakarovitch, Dominique Touchard. Clinical team: Clarisse Amani-Bosse, Ignace Ayekoe, Gédéon Bédikou, Nacoumba Coulibaly, Christine Danel, Patricia Fassinou, Apollinaire Horo, Ruffin Likikouët, Hassan Toure. Laboratory team: André Inwoley, François Rouet, Ramata Touré. Psycho-social team: Hortense Aka-Dago, Alphonse Sihé. Social-sciences team: Hélène Agbo, Hermann Brou, Annabel Desgrées-du-Loû, Annick Tijou-Traoré, Benjamin Zanou. Scientific Committee: Stéphane Blanche, Jean-François Delfraissy, Philippe Lepage, Laurent Mandelbrot, Christine Rouzioux, Roger Salamon.

Ethical permissions

The ANRS 1201/1202 Ditrame-Plus study was granted ethical permission in Côte d'Ivoire from the ethical committee of the National AIDS Control Programme, and in France from the institutional review board of the French Agence Nationale de Recherches sur le Sida (ANRS).

Conflict of interest

None of the authors had any conflict of interest to declare.

Author Contributions

Study concept and design: VL, MTK, FD. Field work and data collection: RB, LB, DKE, IV. Statistical analysis: CS, VL. Interpretation of results: RB, VL, CS. First drafting of the manuscript: VL. Critical revision of the manuscript for important intellectual content: RB, VL, CS. Obtained funding: FD, VL.

Table 1: Prenatal determinants for refusing the formula-feeding option among pregnant women included in the ANRS 1201/1202 Ditrame-Plus cohort and who expressed their infant-feeding choice before delivery (N=256/565). Logistic regression. Univariate analysis.

Variable	N	% Refusal	Odds Ratio	95% Confidence Interval	P
Live with her partner	379	48.3	1.44	1.01-2.06	0.04
Live with her family in law	139	48.9	1.21	0.83-1.78	0.32
Co-spouse	130	52.3	1.44	0.97-2.13	0.07
Ethnic group	565				<0.0001
Akan	210	37.6	0.23	0.12-0.45	
Krou	98	30.3	0.17	0.08-0.35	
Mande North	65	56.9	0.51	0.23-1.10	
Mande South	32	37.5	0.23	0.09-0.58	
Gur	83	60.2	0.58	0.28-1.22	
Other Ivoirian	23	39.1	0.25	0.09-0.69	
Foreigner	54	72.2	1	Baseline	
Muslim	203	58.1	2.24	1.58-3.18	<0.0001
Education level	565				<0.0001
No schooling	204	58.8	3.25	2.07-5.12	
Primary schooling	220	42.3	1.67	1.07-2.61	
Secondary schooling	141	30.5	1	Baseline	
Personal income	287	46.7	1.12	0.80-1.56	0.50
Collective housing	369	51.0	1.96	1.37-2.80	0.0002
Electricity at home	546	44.9	0.59	0.23-1.49	0.26
Type of access to water	565				0.0001
Individual tap	176	32.4	1	Baseline	
Walking distance tap	118	49.1	2.02	1.25-3.26	
Collective tap	271	52.0	2.26	1.52-3.36	
WHO clinical staging	565				0.41
1	191	48.7	1	Baseline	
2	227	44.9	0.86	0.58-1.26	
3	143	42.7	0.75	0.48-1.15	
4	4	0	-	-	
Maternal CD4 level (cells/mm3)	563				0.67
0-199	97	44.3	1.18	0.81-1.73	
200-499	288	46.9	1.07	0.65-1.76	
≥500	178	42.7	1	Baseline	

Centre					<0.0001
Abobo	437	50.3	1	Baseline	
Yopougon	128	28.1	0.39	0.25-0.59	
Sharing HIV status with someone else before delivery	229	33.2	0.43	0.30-0.61	<0.0001
Inclusion date (six-month periods)	565				0.078
March/Aug 2001	99	34.3	0.56	0.34-0.93	
Sept 2001/ Feb 2002	114	50.9	1.11	0.70-1.77	
March/Aug 2002	159	44.6	0.87	0.57-1.32	
Sept 2002/ 6th March 2003	193	48.2	1	Baseline	
Gestational age	565		1.03	0.95-1.11	0.47
Number live born	565		1.09	0.98-1.22	0.11
Maternal age	565		1.00	0.97-1.03	0.95

Table 2: Prenatal determinants for refusing the formula-feeding option among pregnant women included in the ANRS 1201/1202 Ditrame-Plus cohort and who expressed their infant-feeding choice before delivery (N=561). Logistic regression. Multivariate analysis.

Variable	N	Odds Ratio	95% Confidence Interval	P
Live with her partner	376	1.53	1.03-2.28	0.03
Muslim	203	1.54	1.04-2.30	0.03
Education level	561			0.003
No schooling	204	2.40	1.45-3.98	
Primary schooling	216	1.53	0.95-2.47	
Secondary schooling	141	1	Baseline	
Centre	561			<0.0001
Abobo	433	1	baseline	
Yopougon	128	0.32	0.19-0.54	
Sharing HIV status with someone else before delivery	229	0.45	0.31-0.65	<0.0001
Inclusion date (six-month periods)	561			0.0001
March/Aug 2001	97	0.26	0.14-0.46	
Sept 2001/ Feb 2002	113	0.55	0.32-0.95	
March/Aug 2002	158	0.58	0.36-0.94	
Sept 2002/ 6th March 2003	193	1	Baseline	

Table 3: Description and determinants of the postnatal failure of formula-feeding practice in the formula-feeding among women in the formula-feeding group in the ANRS 1201/1202 Ditrame-Plus cohort (N=46/295). Logistic regression. Univariate analysis.

	N	%	% Failure	Odds Ratio	95% Confidence Interval	P
Baseline maternal variables						
Prenatal formula-feeding choice	267	91	15.7	1.12	0.37-3.39	0.84
Live with her partner	186	63	14.5	0.80	0.42-1.53	0.51
Live with her family in law	68	33	13.2	0.78	0.36-1.72	0.54
Co-spouse	56	19	16.1	1.04	0.47-2.31	0.91
Muslim	69	24	18.8	1.34	0.66-2.73	0.41
Education level	295					0.30
No schooling	75	25	21.3	1.71	0.76-3.82	
Primary schooling	125	43	13.6	0.99	0.45-2.16	
Secondary schooling	95	32	13.7	1	baseline	
Personal income	145	49	13.1	0.69	0.36-1.30	0.24
Collective type of housing	173	59	15.0	0.90	0.48-1.70	0.75
Electricity at home	285	97	15.8	1.69	0.21-13.6	0.62
Type of access to water	295					0.87
Individual tap	113	38	14.2	1	baseline	
Walking distance tap	55	17	18.2	1.35	0.57-3.20	
Collective tap	127	45	15.7	1.13	0.56-2.31	
Centre	295					0.34
Abobo	207	71	16.9	1	baseline	
Yopougon	88	29	12.5	0.70	0.34-1.45	

Inclusion date (six-month periods)	295					0.97
March/Aug 2001	63	22	15.9	1.12	0.46-2.70	
Sept 2001/ Feb 2002	51	17	17.6	1.27	0.51-3.17	
March/Aug 2002	84	28	15.5	1.09	0.48-2.46	
Sept 2002/ 6th March 2002	97	33	14.4	1	baseline	
WHO clinical staging	295	295				0.53
1	96	33	13.5	1	baseline	
2	119	40	15.1	1.14	0.53-2.46	
3	77	26	19.5	1.54	0.68-3.48	
4	3	1	0	-	-	
Maternal CD4 cell count (/mm3)	295					0.58
0-199	56	19	19.6	1.60	0.66-3.86	
200-499	141	48	15.6	1.21	0.58-2.53	
≥500	98	33	13.3	1	baseline	
Viral load (log10)	289			1.12	0.80-1.57	0.52
Sharing HIV status with someone else before delivery	147	50	12.9	0.66	0.35-1.26	0.21
Gestational age	295			0.93	0.81-1.07	0.33
Nb live born	295			1.13	0.91-1.39	0.26
Age	295			0.98	0.91-1.04	0.48
Delivery variables						
Multiple birth	18	6	33.3	2.88	1.02-8.10	0.04
C-section	17	6	11.8	0.69	0.15-3.12	0.63
Low birth weight (<2.5kg)	40	14	30.0	2.69	1.25-5.79	0.01