Original Article

Obstetrical, maternal characteristics and outcome of HIV-infected rapid progressor infants at Yaounde: a retrospective study

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Background: Rapid progressors are exposed to HIV infection at an early stage of life, and the prognosis is poor without treatment. Reducing the proportion of infants who are rapid progressors, require strengthening strategies to achieve the highest level of performance for the PMTCT program.

Methods: This was a retrospective study carried out on HIV infected infants aged less than 12 months, clinically classified stage 4 (WHO) or having CD4 count <25%. We described maternal and obstetrical characteristics of HIV-infected rapid progressors using univariate and bivariate analysis. Patients' survival was monitored from the inclusion time to the end of the study. We then estimated their probability of survival with or without anti-retroviral (ARV) treatment from birth using the Kaplan-Meier method.

Results: The characteristics of the mothers of the 150 rapid progressors infants we included were: low level of education (OR=3.87; P=0.016), CD4 count less than 200/mm^3 (OR=43.3; P=0.000), absence of ARV prophylaxis (OR=6.02; P=0.043), or treatment with HAART (OR=5.74; P=0.000) during pregnancy. In the children, the most important findings were lack of co-trimoxazole prophylaxis (OR=11.61; P=0.000) and antiretroviral prophylaxis (OR=2.70; P=0.0344). The survival rate was 84.3% in infants who were receiving HAART as opposed to 43.3% in those who were not (P<0.05).

Conclusions: HIV infected women who are eligible should start antiretroviral treatment prior to a pregnancy, in order to improve their immunological status. This measure associated to cotrimoxazole prophylaxis and ART could improve their survival.

Keywords: HIV; infection; rapid progressors; infants; characteristics

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Introduction

The proportion of HIV-infected who are rapid progressor has decreased with the improvement of the quality of Prevention of Mother to Child Transmission (PMTCT), and more specifically with early management of the mother and child (1). In 2011, the demographic health survey conducted in Cameroon showed that the HIV seroprevalence in women aged 15–49 years who were pregnant during the survey was 5.6% (2). However, the performance level of the PMTCT program is rather low nationwide, with only 21.4% of the HIV infected pregnant women receiving anti-retroviral (ARV) prophylaxis (3). Many HIV exposed infants born to mothers who have

received PMTCT interventions may have missed out some of the interventions that target infants. In fact, about 74.3% of infants did not receive any ARV prophylaxis according to the report of the ministry of public health (3). A study carried out in the Eastern Region of Cameroon showed that 65.2% of exposed infants and 91.1% of mothers did not receive any ARV prophylaxis for PMTCT (4).

Pediatric HIV infection is most often transmitted vertically , either during pregnancy, delivery or during breastfeeding (5-10). Newell *et al.* found that without any intervention, 35.2% of HIV infected children will die at the end of the first year and 52.5% by two years in resource limited countries (11). Before that Blanche *et al*. showed that 44% of HIV-1 infected infants born to mothers with severe disease at delivery, will die during the first 18 months of life as a result of HIV encephalopathy and opportunistic infections (12). Rapid progressors are infants who develop severe signs of AIDS very early in life usually leading to death for most of them (13,14). Many factors are described in literature concerning HIV-infected rapid progressors (15-18). It has been proven that there is a relationship between high maternal viral load and severe immunodeficiency, and high viral load in infants (15,19-22). The severity of immunosuppression, and high viral loads in infants (23-25) are associated with rapid progression of HIV infection. On the contrary, maternal treatment even with prophylactic regimen, would indirectly reduce the progression of the disease in the infant (15,16,19,26). Some associated factors could be found in our milieu because of concurrent illness. The objective of our study was to explore factors which can help in diagnosing rapid progressor children and their outcome.

Methods

Study framework

A retrospective study was carried out to identify rapid progressor infants seen between January 2010 and February 2012 at the Mother and Child Centre of the Chantal Biya Foundation (CME-CBF). The CME-CBF is a pediatric centre which handles the largest cohort of children on ARVs in Cameroon. HIV testing of children less than 18 months was done using DNA/RNA PCR. The PCR was done at the Centre Pasteur du Cameroun in the framework of the ANRS Pediacam study (27) and at the Chantal Biya International Research Center (CBIRC) (28). The children were referred to the CME-FCB either for diagnosis of HIV in those suspected to be infected or for further management of the already diagnosed HIV infection. The others were HIV exposed infants followed up in PMTCT. Patients are managed at the study site following the national guidelines for HIV exposed and infected children (29).

Study population

HIV-infected infants less than 12 months old received and followed up at the HIV treatment centere of the CME-FCB were included in this study. We excluded asymptomatic HIV-infected subjects with no available CD4 count and also exposed infants of HIV-infected mothers without PCR result.

Procedure and data collection

We reviewed the medical records of the HIV-infected children from the database of the site. According to our inclusion criteria, we selected those in whom the signs and symptoms corresponded to stage 4 of the WHO classification or who had CD4 counts below 25% no matter their clinical stage, whether they had been on ARV therapy or not. Mothers or guardians who accompanied their infants to routine consultations were interviewed on the pregnancy that led to the birth of the child. Data which could not be obtained from mothers' interview (mothers who died or were absent) were collected from the medical records of the patients. Reasons why PMTCT was not carried out were sought. We collected socio-demographic data of the mothers such as: age, level of education, social status. We then obtained information concerning the maternal obstetrical history. This was the number of antenatal clinics (ANCs) attended, the existence of any pathologies during the pregnancy and PMTCT measures carried out, as well as the perinatal history. We also found out about cases of death of siblings.

Concerning the infants, we recorded their age, sex, immunization status, the psychomotor development, comorbid conditions and prior hospitalisations. We also evaluated their nutritional status and found out whether they received Cotrimoxazole and ARV prophylaxis, feeding practices, biological analysis (CD4 count, and viral load).

Main outcome and other variables definitions

"Rapid progressor infant" was defined as any HIV-infected infant whether on HAART or not who developed during

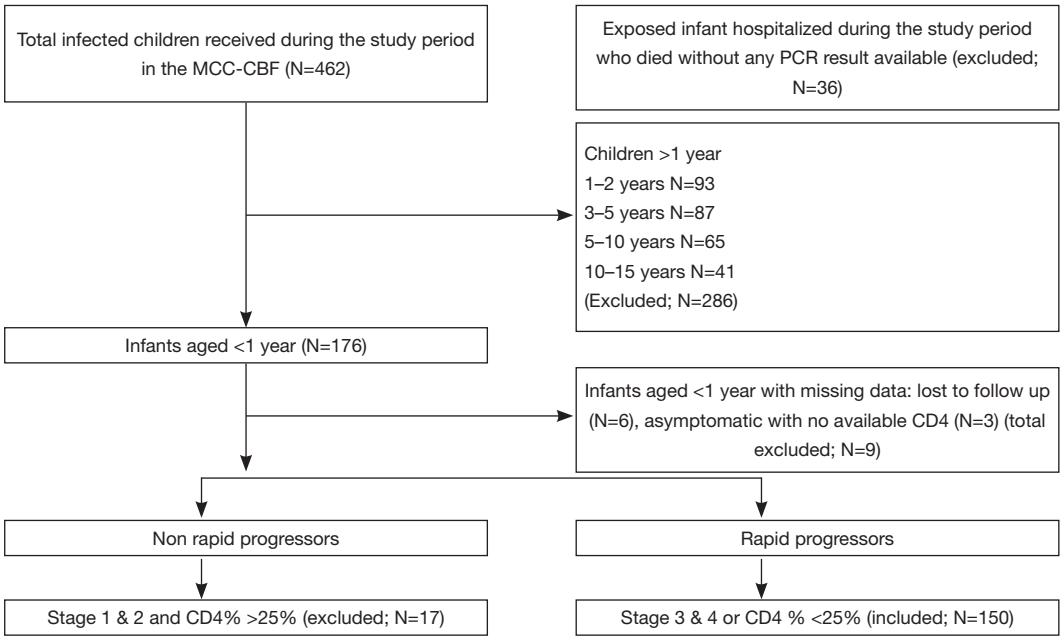

Figure 1 A flow diagram of enrolment of HIV-infected rapid progressor infants.

his first year of life, a sign which classifies him in clinical stage 3 or 4 or a severe immunodeficiency (% CD4 <25) or both (30). Patients survival during the study period was evaluated. We then estimated their probability of survival with or without ARV treatment from birth to the end of the study using the Kaplan-Meier method.

Other variables as mentioned above were used. The feeding method were defined as; infant formula feeding, breastfeeding or mixed when other food, solid or liquid was given in addition to breast milk. Protected breastfeeding was described when the mother was receiving or had received prophylactic ARVs and as well as the infant, for up to one week following the end of the breastfeeding. Their clinical and immunological stages were determined using the WHO classification. Infants were divided into two groups; minor immunodeficiency (those in stage 1 and 2), and major immunodeficiency (those in stages 3 and 4).

Statistical analysis

Data was analysed using the Epi Info 7 software and Microsoft Excel 2010. Through the univariate analysis of maternal and infant characteristics, we described the categorical variables in frequencies and percentages. Medians and interquartile ranges were used for continuous variables. Bivariate analysis consisted of estimating the odds ratio measuring the obstetrical, mothers and infants characteristics of the HIV-infected rapid progressors within the 95% confidence intervals. We use the Log-rank test to calculate P value which we analysed. P values <0.05 were considered statistically significant.

Ethical considerations

Our study was approved by the Institutional Ethics and Research Committee of the Faculty of Medicine and Biomedical Sciences of the University of Yaounde I. A written or verbal informed consent was obtained from parents or guardians prior to their interview and data collection. Both clinical records and laboratory results were kept confidential.

Results

Socio-demographic data

In all, 462 HIV-1-infected children were received on site during the study period; no case of HIV-2 was recorded. Among the subjects, we identified 176 HIV-1 infected infants aged less than 12 months. Of the 150/(32.5%) HIV-infected children who fulfilled our inclusion criteria, 85.2% of them were rapid progressors (*Figure 1*). The median age

Table 1 Maternal characteristics of rapid progressor infants

Variables	Modalities	N (%)
Age at delivery in years (n=150)	≤20	10 (6.7)
	21–29	90 (60.0)
	30–39	44 (29.3)
	≥40	6 (4.0)
Education level or training (n=131)	Secondary and higher	111 (84.7)
	Illiterate or primary	20 (25.3)
Profession (n=131)	Housewife	60 (45.8)
	Liberal	33 (25.2)
	Student	22 (16.8)
	Employee	16 (12.2)
Marital status (n=131)	Unmarried	56 (42.7)
	Cohabitation	55 (42.0)
	Married	17 (12.7)
	Widow	3 (2.6)
Time of HIV screening with regard to the pregnancy (n=150)	After delivery	80 (53.3)
	Antenatal and during the 1st trimester	26 (17.3)
	2nd trimester	22 (14.7)
	3rd trimester	13 (8.7)
	During labor	9 (6.0)
Number of ANC (n=150)	1–4	75 (50.0)
	>4	66 (44.0)
	None	9 (6.0)
Place of ANC (n=122)	Health center	73 (59.8)
	District or 2nd and 3rd reference hospital	49 (40.2)
CD4 level/mm^3 during pregnancy (n=41)	<200	12 (29.3)
	200–499	15 (36.6)
	≥500	14 (34.1)
ARV treatment during pregnancy (n=150)	None	105(70.0)
	Prophylactic	30 (20.0)
	HAART	15 (10.0)
Hospitalization during pregnancy (n=131)	Yes	62 (47.3)
	No	69 (52.7)
Mode of delivery (n=150)	Normal delivery	145 (96.7)
	Caesarean section	5 (3.3)
Place of birth (n=150)	Health center	78 (52.0)
	District or 2nd and 3rd reference hospital	53 (35.3)
	House	19 (12.7)

ANC, antenatal care; ARV, anti-retroviral.

was 6 months with an interquartile range [4; 10 months] during the enrolment. Of the 150 rapid progressors, 19 (12.7%) had lost their mothers; 13 (8.7%) their fathers and 4 (2.7%) both parents when the diagnosis of HIV infection was made. At enrolment, 10.7% were accompanied by a guardian. Mean age of the living mothers was 27 years, ranging from 18 to 43 years, 45.4% were single or 42.0% were cohabiting (not officially married). Almost all of them 97.7% (128/131) were literate with 61.0% having attained secondary school level and half (45.8%) were housewives (*Table 1*). Most of the children who were rapid progressor 80.7% (121/150) had siblings with 50.7% of them having more than 3 siblings. In 11.3% of cases, there was a history of death of a sibling occurring between the ages of 3 to 16 months with a median age of 8 months; their HIV status as well as that of their mothers were unknown at the time of death.

Antenatal history and prevention of mother to child transmission of HIV (PMTCT)

Most of the mothers interviewed (65.4%) started ANC during the second trimester, others either during the first (11.3%) or the third (17.3%) trimester, while some (6%) never attended ANC. About 47.2% (62/131) of mothers were hospitalized during their pregnancy because of one or a combination of pathologies including gastro-enteritis (59.7%), pulmonary infections (48.4%), malaria (43.5%); genital and urinary tract infections (20.9%) and pulmonary tuberculosis (19.4%). PMTCT measures were not carried out in 2/3 of these mothers, 105 pregnant women (70.0%) did not take any ARV prophylaxis. Most of them did not know their HIV status. The status for 80 (53.3%) of them was discovered after delivery, and for others when the child was ill. Twenty three mothers (15.3%) knew their HIV status before pregnancy, 35 (23.3%) during pregnancy with 2%, 14.7% and 8.7% during the first, the second and the third trimester respectively. Nine (6.0%) were informed at delivery (*Table 1*). Ignorance of their HIV status, denial of the test results and no ARVs given by health care providers were some of the reasons given for the absence of ARV prophylaxis. Of the 45 mothers who received ARVs, 15 (33.3%) were on HAART, 9 of whom started ARV before; 5 during pregnancy and 1 after childbirth. Others 30/45 (66.7%) received ARV prophylaxis, 10 (33.3%) of whom received single dose Nevirapine during labour. Some mothers, 19 (12.7%) gave birth at home. Only 41 (27.3%)

Table 2 Characteristics of rapid progressor HIV-infected infants

Variables	Modalities	N (%)
Age group (months) (n=150)	≤3	33 (22.0)
	4–6	42 (28.0)
	7–9	34 (22.7)
	10–12	41 (27.3)
History of premature birth (n=150)	Yes	20 (13.3)
	No	130 (86.7)
Birth weight in kilogram (n=125)	<2.5	21 (16.8)
	2.5–3.5	62 (49.6)
	3.5–5	42 (33.6)
ARV prophylaxis (n=150)	Yes	39 (26.0)
	No	111 (74.0)
Cotrimoxazole prophylaxis (n=150)	Yes	15 (10.0)
	No	135 (90.0)
Feeding option at birth (n=150)	Exclusive breastfeeding	40 (26.7)
	Infant formula	50 (33.3)
	breastfeeding mixed with formula	52 (34.6)
	protected breastfeeding	8 (5.4)
Having received HAART (n=150)	Yes	97 (64.7)
	No	53 (35.3)

ARV, anti-retroviral.

Table 3 Maternal and child characteristics of HIV-infected rapid progressor infants; Bivariate analysis

Variables	N	OR	P	CI (95%)
Maternal related characteristics				
Not educated or primary school	20	3.87	0.016	1.00–12.26
CD4 <200/mm^3 during pregnancy	12	43.31	0.000	6.20–299.12
No ARV prophylaxis during pregnancy	105	6.02	0.043	1.63–52.70
HAART treatment during pregnancy	15	5.74	0.000	1.01–50.23
<4 antenatal care	84	1.32	0.587	0.47–3.66
Hospitalization during pregnancy	62	1.36	0.526	0.50–3.62
Maternal death	19	3.04	0.261	0.38–24.23
Infant related characteristics				
No cotrimoxazole prophylaxis	135	11.61	0.000	3.50–37.65
No ARV prophylaxis	39	2.70	0.0344	1.03–7.25
Viral load >6 $\log_{10}$ copies/mL	67	1.68	0.3760	0.58–5.57
Birth weight <2,500 g	21	0.37	0.0882	0.16–1.22
Breastfeeding mixed with formula	52	1.36	0.5356	0.53–3.74
Exclusive breastfeeding	40	1.96	0.2625	0.60–6.07

ARV, anti-retroviral.

CD4 counts performed during pregnancy were reported and these showed a severe immunodeficiency with CD4 count <200/mm^3 for 12 of them (29.3%).

Significant maternal factors associated with subjects were the low level of education (OR=3.87; P=0.016), CD4 count less than 200/mm^3 during pregnancy (OR=43.3; P=0.000), absence of ARV prophylaxis (OR=6.02; P=0.043), or treatment with HAART (OR=5.74; P=0.000).

Characteristics of the rapid progressor infants

At enrolment, 87 infants (58.0%) were in clinical stage 4 while the others were selected based on severe immune deficiency. The viral load was available only in 79 (52.7%) infants and the values ranged between 111.3 and 663 $\log_{10}$ copies/mL with an average of 87.7 $\log_{10}$ copies/mL. Only 39 rapid progressors (26.0%) had received ARV prophylaxis at birth (*Table 2*), more than 3/4 (76.9%) of whom had been on bitherapy with Zidovudine and Nevirapine, the rest received monotherapy; 12.8% received Nevirapine and 10.7% Zidovudine.

In infants, the most significant events were the absence of Cotrimoxazole prophylaxis (OR=11.61; P=0.000) and antiretroviral prophylaxis (OR=2.70; P=0.0344); (*Table 3*).

Outcome of the rapid progressors

Death occurred in 52/150 (34.7%) of the patients during the study period, at a median age of 7 months (*Table 4*). The survival rate was higher (84.3%) in infants who were receiving ARV treatment (P<0.05) as opposed to 43.3% in those who were not (*Figure 2*).

Table 4 Outcome of rapid progressor infants with regard to their clinical stages

Clinical stage	Alive N (%)	Death N (%)	Lost to follow-up N (%)	Total
1	11 (13.7)	1 (12.5)	1 (5.6)	13
2	5 (6.3)	1 (12.5)	1 (5.6)	7
3	29 (36.3)	11 (13.7)	3 (16.7)	43
4	35 (43.7)	39 (48.7)	13 (72.2)	87
Total	80 (100.0)	52 (100.0)	18 (100.0)	150

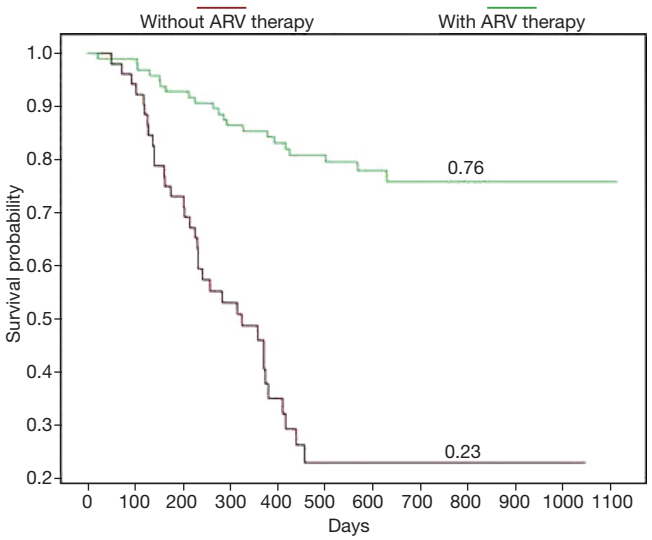

Figure 2 Survival curve of HIV-infected rapid progressor infants.

Discussion

This retrospective study described the HIV-infected rapid progressors with regards to the mothers' obstetrical characteristics and those of the children. The proportion of the rapid progressor was high in our study. Our study has not been performed on a cohort of infant. We recruited at a specialized HIV/AIDS unit where most of the children were symptomatic at referral. Most of them came either from our admission units or from others health facilities for confirmation of their HIV status or for follow up. Some were HIV exposed infants followed in the PMTCT unit. These could have introduced some bias.

We found patients at clinical stage 1 & 2 with a severe immunological deficiency (CD4 count <25%). Some had severe clinical stage but no profound immune-depression. We also described the socio-demographic background of the mother and infant couple and found out whether they benefited from PMTCT interventions. Only 12.2% of the mothers were employed. The socio-demographic conditions were poor for many; in fact, 12.7%, 8.7% and 2.7% of infants had lost their mothers, fathers or both parents respectively. Such conditions increase the vulnerability of the subjects to illnesses and death (31). The maternal factors that were significantly associated with advanced WHO clinical stage of the rapid progressors were a CD4 count <200/mm^3, absence of ARVs prophylaxis or not being on HAART. Previous studies have shown that severe immune deficiency in mothers was associated with early poor progression of the HIV in infants (16,32). The same would be true with a high maternal viral load during delivery (33,34). Ideally, testing of women of child-bearing age and pregnant women could permit early HIV screening and the initiation of ARV treatment or the PMTCT program in case of infection. Early detection of HIV infection in mothers as from the 14th week of gestation and of every exposed child at birth are cost-effective (35). In our study, 65.4% of the pregnant women started ANC during the second trimester and 53.3% had their HIV screening performed after delivery and for some when the children were ill. Hence, most (70.0%) of them did not receive any ARV prophylaxis during pregnancy meanwhile its effectiveness has been proven in the reduction of the rate of rapid disease progression in children (15,16,19,26). Thus, the rapid progressors seem to be particularly associated with such situations in our study (OR=6.02; P=0.043). It has been demonstrated that HAART is more effective in the prevention of severe clinical forms in children than ARV prophylaxis (11,15). In our population however, the benefits of HAART during pregnancy was not remarkably associated with rapid progressor infants. Only 15 women received HAART during pregnancy (*Table 1*). We did not investigate the existence of a relationship between the onset of treatment and the gestational age. One could imagine cases in which the HAART had not yet induced significant effects on the immunity of some mothers, particularly those who were severely immuno-compromised during the pregnancy. Analysis of rapid progressors' specific conditions revealed an association between the absence of prophylaxis with cotrimoxazole (P=0.000, OR=11.61), or ARVs (P=0.0344, OR=2.70), and the severity of the clinical and immunological presentation in this study. Indeed, cotrimoxazole can

prevent under certain conditions, severe infections in infants infected with HIV. It can reduce mortality by 43% and hospitalizations by 23% (36,37).

The mortality rate was higher (34.7%) in our population (*Table 4*), compared to that found in Nepal (38). It others setting very high mortality rate where found in infants who were not on ARV compared to those receiving ARV treatment (14). Death occurred in our study at a median age of 7 months; HIV infection increased the death rate before the age of 2 years considerably (39,40). The survival rate was low (43.3%) in children who were not treated, against 84.3% in those on ARV treatment. It has been demonstrated that HAART increases survival in approximately 95% of patients; meanwhile, death is almost inevitable for those without treatment (41). For this reason, authors suggested that HAART should be given as early as possible for all HIV-infected children (1,13,42).

Conclusions

In our study, mothers were often not aware of their HIV status and some did not have access to PMTCT services. According to authors, such mothers constitute a target population, for whom early diagnosis of their children is important (43). HAART before pregnancy for women eligible to treatment would improve their CD4 count before pregnancy. It must be associated to cotrimoxazole and ART prophylaxis in infants, as well as HAART in infant with a positive PCR in order to improve their survival rate.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Informed Consent: For each patient, parent's or guardian's written or the verbal consent was obtained prior to the enrolment of their infant.

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