Virologic Response to Early Antiretroviral Therapy in HIV-infected Infants

Evaluation After 2 Years of Treatment in the Pediacam Study, Cameroon

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Introduction: Little is known about virologic responses to early antiretroviral therapy (ART) in HIV-infected infants in resource-limited settings. We estimated the probability of achieving viral suppression within 2 years of ART initiation and investigated the factors associated with success.

Methods: We analyzed all 190 infants from the Cameroon Pediacam who initiated ART by 12 months of age. The main outcome measure was viral suppression (<1000 copies/mL) on at least 1 occasion; the other outcome measures considered were viral suppression (<400 copies/mL) on at least 1 occasion and confirmed viral suppression (both thresholds) on 2 consecutive occasions. We used competing-risks regression for a time-to-event analysis to estimate the cumulative incidence of outcomes and univariate and multivariate models to identify risk factors.

Results: During the first 24 months of ART, 20.0% (38) of the infants died, giving a mortality rate of 11.9 deaths per 100 infant-years (95% confidence interval: 8.1–15.7). The probability of achieving a viral load below 1000 or 400 copies/mL was 80.0% (69.0–81.0) and 78.0% (66.0–79.0), respectively. The probability of virologic suppression (with these 2 thresholds) on 2 consecutive occasions was 67.0% (56.0–70.0) and 60.0% (49.0–64.0), respectively. Virologic success was associated with not having missed any doses of treatment before the visit, but not with socioeconomic and living conditions.

Conclusion: Many early treated children failed to achieve virologic suppression, likely due to a combination of adherence difficulties, drug dosing and viral resistance, which highlights the need for routine viral load monitoring. The high infant mortality despite early ART initiation needs to be addressed in sub-Saharan countries.

Key Words: HIV-infected infants, antiretroviral treatment, virologic success

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Antiretroviral therapy (ART) has markedly reduced morbidity and mortality in children,[1–3] transforming pediatric HIV infection from a rapidly fatal illness to a chronic disease. Moreover, early ART, initiated in the first few months of life, has been shown to be clinically beneficial, leading the World Health Organization and national guidelines to recommend ART initiation in all infants and young children, regardless of immunologic or clinical stage.[4–6]

The most recent World Health Organization recommendations are now being implemented in sub-Saharan Africa. The number of children taking these drugs is thus increasing,[7–9] but little is known about their mid- and long-term virologic responses. In a large European collaborative cohort of HIV-infected adults and children from 1998 to 2006, the weakest virologic responses were reported in those of children under 2 years of age with 34% having a viral load (VL) <400 copies/mL after 12 months of ART.[10] Virologic suppression after 12 months of ART initiated before 1 year of age was reported in 62% of HIV-infected infants living in Europe and treated between 2004 and 2008,[11] and in 56% of such children in Southern Africa.[12]

The Pediacam cohort study was designed to evaluate feasibility and outcomes of systematic ART initiated as soon as possible after diagnosis, in infants testing positive for HIV before 6 months of age, in 2 major urban areas of Cameroon as described previously.[13,14] We investigated the probability of virologic success (VS) within 2 years of early ART initiation in HIV-infected infants and the factors associated with treatment success.

METHODS

The Agence Nationale française de Recherches sur le Sida et les hépatites virales12140 Pediacam Study

Pediacam prospectively enrolled HIV-infected infants in 2 phases between November 2007 and October 2011 at 3 referral hospitals in Cameroon located in Yaoundé and Douala.[13,14] In the

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first phase, infants born to HIV-infected and HIV-uninfected mothers were matched for sex and recruitment site during the first week of life and followed until 14 weeks of age. HIV-exposed infants underwent HIV testing at 6 weeks of age with results available at 10 weeks of age; infants testing positive were retested for confirmation. HIV-negative breastfed infants were retested 6 weeks after weaning. All HIV-infected infants and subsamples of uninfected HIV-exposed and HIV-unexposed infants were eligible for the second phase of 5-year follow-up. During phase 2, HIV-infected infants diagnosed after the first week of life but before 7 months of age were also enrolled.

Overall, 210 HIV-infected infants were included in this second phase. ART was initiated upon confirmation of HIV status: zidovudine (or abacavir or stavudine) + lamivudine, combined with nevirapine or ritonavir-boosted lopinavir for infants with nevirapine exposure as part of prevention of mother-to-child transmission. HIV VL, as determined by RT-PCR (Biocentric, Bandol, France), and additional biologic and clinical parameters were assessed at inclusion and then every 3 months after ART initiation. At the same times, caregivers completed a standardized questionnaire about family living conditions and adherence to ART.

Study Population

We retained the 190 infants who began ART at or before 12 months of age from the 210 infants included in phase 2 of the Pediacam study (Fig. 1). We excluded infants who died (n = 12), moved or were lost to follow-up (n = 5) before starting ART or who began ART after 12 months of age (n = 3).

Variables

The main outcome variable was the achievement of at least 1 VL <1000 copies/mL within the first 2 years of ART treatment, defined as VS. More stringent definitions were considered as secondary outcomes: VL <400 copies/mL[15–19] and confirmed virologic success (CVS) for each threshold, defined as virologic suppression at 2 consecutive visits no more than 6 months apart. The VL measures analyzed were restricted to those performed at scheduled quarterly measurements ±1.5 months, between 3 and 24 months after ART initiation.

Exposure variables included study design elements (site, mode of inclusion in Pediacam—at or after birth), baseline living conditions, clinical characteristics and history of ART (including history of nevirapine neonatal prophylaxis, type of first ART regimen, availability of running water, electricity, refrigeration at home, VL and CD4 cell percentage) and adherence, as reported by the caregiver at each visit (number of doses missed in the last 3 days). Infants were considered nonadherent if at least 1 dose was missed.[20]

Statistical Analysis

Competing-risks regression was used for time-to-event (VS) analysis in the presence of competing risks of death.[21,22] Date at ART initiation (T_0) was used as the baseline. Data were right censored at the date of the first event (VS) or death before VS, or at the last VL measurement within 24 months of baseline (T_0) if neither VS nor death occurred before this date. For the analysis of secondary outcomes for "confirmed virologic success," we did not consider a VL <1000 (or 400, according to threshold considered) copies/mL with no subsequent confirmatory VL measurement as an event, even if measured at the last point-of-care evaluation 24 months after baseline; in this situation, the data were right censored at the date of this last available measure.

Competing-risks regression curves were plotted to estimate the cumulative incidence of outcomes. Univariate and multivariate competing-risks regressions were fitted to assess the association between VS and exposure variables. Hazard ratios (HRs) across categories of exposure variables were compared in Wald test. All multivariate models were systematically adjusted for sampling design variables (mode of entry, clinical site and calendar year at inclusion) and/or known risk factors for treatment failure: age and type of regimen at ART initiation; VL, type of caregiver and availability of refrigeration at home at baseline; caregiver-reported missed antiretroviral doses in the last 3 days, as a time-dependent covariate. The other noncollinear baseline variables associated with VS in univariate analysis with *P* values ≤0.20 were included in the

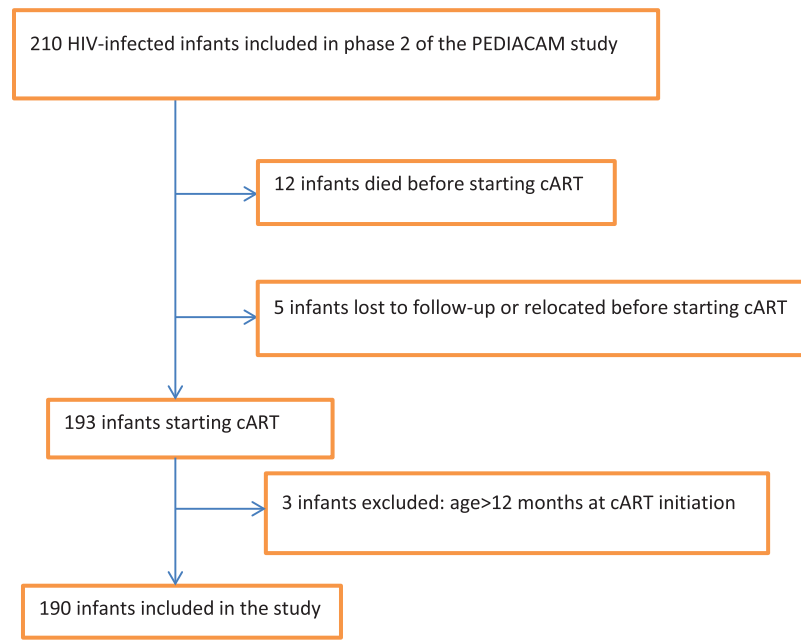

FIGURE 1. Flowchart of HIV-infected infants beginning ART (ANRS-Pediacam Study, 2008–2013, Cameroon). full color online

TABLE 1. Baseline Characteristics of the HIV-infected Study Population at cART Initiation (ANRS-Pediacam Study, 2008–2013, Cameroon)

Variables	% (n) or Median (IQR)
Male (N = 190)	43.7 (83)
Mode of inclusion (N = 190)	
At birth	31.6 (60)
After birth but before 7 months of age	68.4 (130)
Site of cART delivery (N = 190)	
CME/FCB	49.5 (94)
HLD	21.1 (40)
CHE	29.4 (56)
Father's HIV status (N = 190)	
HIV positive	23.7 (45)
HIV negative	22.6 (43)
Unknown	53.7 (102)
Mother receiving cART (N = 190)	20.5 (39)
Father receiving cART (N = 190)	19.0 (36)
Infants living with (N = 190)	
Both parents	52.1 (99)
Mother only	35.3 (67)
Father only	0.0 (0)
Other relatives	12.6 (24)
Family size ≤5 people (N = 190)	47.4 (90)
Refrigerator at home (N = 190)	49.0 (93)
Running water at home (N = 190)	54.7 (104)
Electricity at home (N = 190)	89.0 (169)
Prior exposure to nevirapine for prophylaxis (N = 190)	78.4 (149)
Clinical presentation at cART initiation	
Weight for age Z score,* median (IQR) (N = 190)	0.2 (0.0–0.4)
History of hospitalization, diarrhea, convulsions or infectious disease (N = 180)†	73.3 (132)
CD4 cell percentage at cART initiation (N = 190)	
<25.0	53.7 (113)
≥25.0	46.3 (77)
Median (IQR)	23.0 (15.0–31.8)
Viral load (log_{10} copies/mL) at cART initiation (N = 190)	
<6.0	25.8 (49)
6.0–6.4	24.2 (46)
6.5–7.0	26.8 (51)
>7	23.2 (44)
Median (IQR)	6.5 (5.4–7.0)
Age at cART initiation (N = 190)	
<3 months	19.4 (37)
3–6 months	61.6 (117)
7–12 months	19.0 (36)
In months, median (IQR)	4.0 (3.0–5.6)
Calendar year at cART initiation (N = 190)	
2008	27.4 (52)
2009	35.3 (67)
2010	23.2 (44)
2011	14.1 (27)
Time from HIV diagnosis to cART initiation (N = 190) (weeks)	
≤2	69.5 (132)
2–6	26.8 (51)
6–12	3.7 (7)
First cART regimen (N = 190)	
Lopinavir based	64.7 (123)
Nevirapine based	34.2 (65)
Three nucleoside reverse transcriptase inhibitors	1.1 (2)

*Weight for age Z score, using WHO curves as reference.

†These data were not provided in full by the healthcare providers.

cART indicates combined antiretroviral therapy; CHE, Centre Hospitalier d'Essos; CME/FCB, Centre Mère et Enfant de la Fondation Chantal Biya; HLD, Hôpital Laquintinie de Douala; IQR, interquartile range; N, total number of subjects; n, number of subjects in the category; WHO, World Health Organization.

initial model and retained in the final backward elimination model if $P \leq 0.10$.

All statistical analyses were performed with STATA 13.0 (StataCorp, College Station, TX).

Ethical Considerations

The ANRS-Pediacam study was granted ethical approval in Cameroon by the National Ethics Committee and in France by the Biomedical Research Committee of the Pasteur Institute of Paris. Caregivers gave written informed consent before participation.

RESULTS

Description of the Study Population

ART was initiated before 12 months of age in 190 HIV-infected infants; 31.6% were included in the study within 1 week of birth, and the others at the time of HIV diagnosis, between 1 week and 7 months of age (Table 1). Most (80.0%) of the infants were enrolled in Yaoundé. Half were living with both parents, 35.3% with their mother only and 12.6% with other relatives. Nearly 90% of the households had electricity; a functional refrigerator and running water were available in 49.0% and 54.7% of households, respectively. ART was initiated at a median age of 4.0 months (interquartile range = 3.0–5.6), with a baseline median CD4 cell percentage of 23.0% (15.0–31.8) and a baseline median VL of 6.5 log_{10} copies/mL (5.4–7.0). The first ART regimen included nevirapine (34.2%) or ritonavir-boosted lopinavir (64.7%), with only 1.1% of infants treated with 3 nucleoside inhibitors (abacavir, zidovudine or stavudine, lamivudine). A single prophylactic dose of nevirapine was administered at birth to 149 infants, 63 of whom received a nevirapine-based first ART regimen.

Mortality

Thirty-eight infants died within 2 years of ART initiation, corresponding to a mortality of 11.9 deaths per 100 infant-years (95% confidence interval: 8.1–15.7) (Fig. 2). Most (34 infants) died before M12, and 68.4%[23] had severe immunosuppression (CD4 <25%) at diagnosis. Death occurred after a median of 3 months of treatment, and the probabilities of death were 18.0% (13.0–24.0) and 20.0% (15.0–26.0) after 1 and 2 years of ART, respectively.

Probability of VS

A competing-risks model showed the probability of attaining a VL <1000 or 400 copies/mL on at least 1 occasion in the first 2 years of ART to be 80.0% (69.0–81.0) and 78.0% (66.0–79.0), respectively. Most successes occurred within 12 months of ART initiation [70.0% (60.0%–80.0%)], with similar median times for the 2 thresholds (6.0 and 6.5 months, respectively).

The probability of confirmed virologic success (CVS) on 2 consecutive occasions was lower, at 67.0% (56.0–70.0) for the 1000 copies/mL threshold and 60.0% (49.0–64.0) for the 400 copies/mL threshold (Fig. 2). Median time to CVS was 7.0 and 12.0 months, respectively.

Factors Associated With VS

The only factor significantly associated with the primary outcome (time to first VL <1000 copies/mL within 2 years of ART initiation) in both univariate and multivariate analyses was not having missed any doses in the 3 days preceding the visit, which was included in the model as a time-dependent variable [adjusted subhazard ratio (asHR) = 1.7 (1.3–2.3); $P < 0.01$] (Table 2). The probability of reporting nonadherence at least once was 52.0% (45.0–59.0) at 2 years of ART.

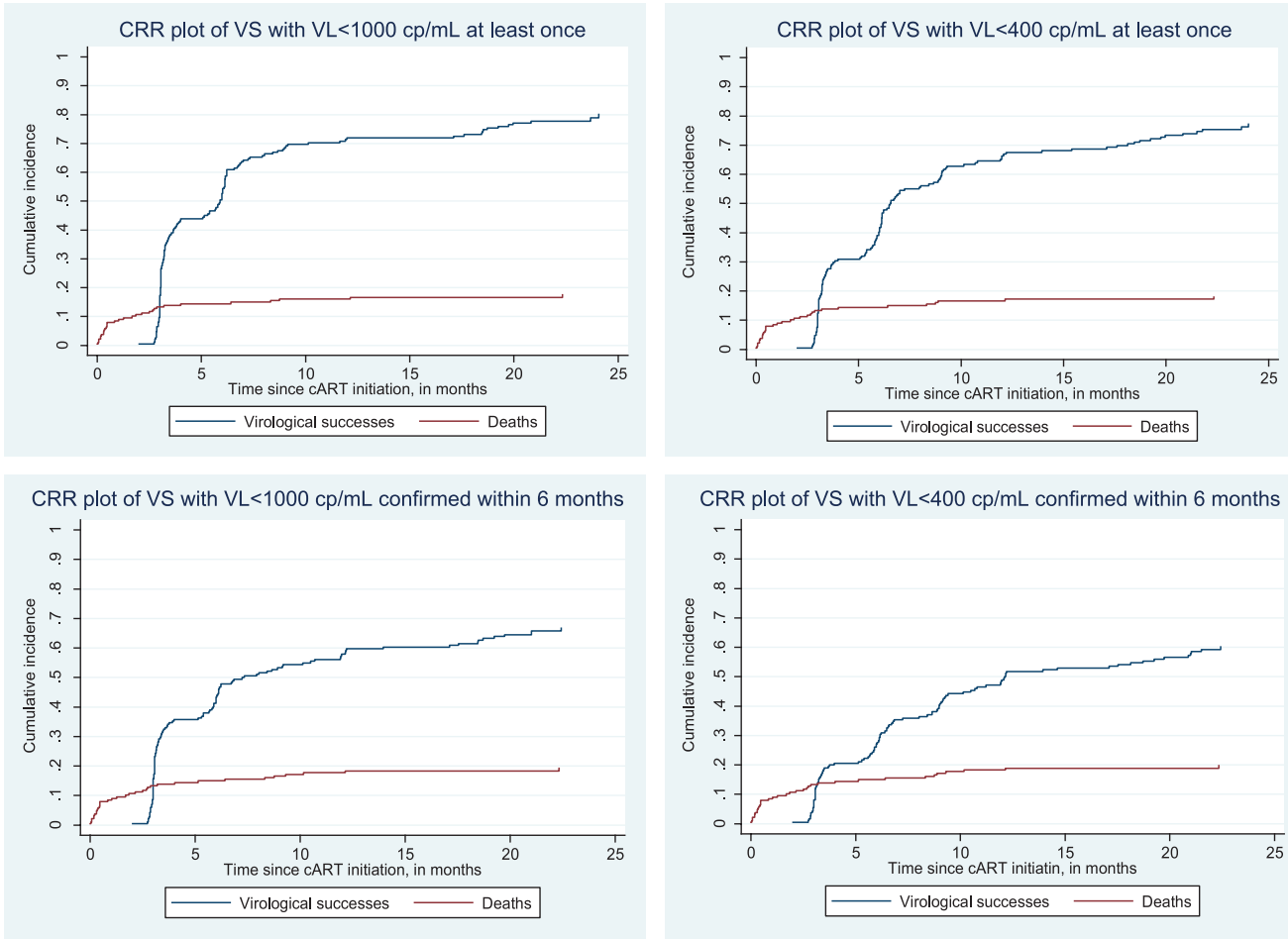

FIGURE 2. Competing-risks regression plots of a first current or confirmed virologic success (viral load <1000 copies/mL at least once) within the first 2 years of ART in infants (ANRS-Pediacam Study, 2008–2013, Cameroon). full color online

In multivariate analysis, there was also a trend toward the association of VS with earlier inclusion period [asHR = 1.4 (1.0–2.0) before 2010 vs. after 2010; $P = 0.06$] and having a refrigerator at home [asHR = 1.3 (1.0–1.8); $P = 0.07$]. The association with adherence was unaffected by refrigerator availability: aHR = 2.1 (1.4–3.2) if a refrigerator was available, and aHR = 1.4 (1.0–2.1) otherwise.

VS was not associated with mode of entry in the study, clinical site, age at ART initiation, history of neonatal nevirapine-based prophylaxis, familial environment and type of carer, pretreatment CD4 percentage or VL. VS did not differ with the type of first ART regimen (including nevirapine or ritonavir-boosted lopinavir), regardless of refrigerator availability [respectively with and without refrigerator: HR = 0.8 (0.5–2.3), $P = 0.34$; HR = 1.0 (0.6–1.7), $P = 0.90$].

The more stringent secondary outcome (time to reach first VL <1000 copies/mL with confirmation at the next measure = CVS) was also associated principally with not having missed any doses in the last 3 days, but also with a lower pretreatment VL, in both univariate and multivariate analyses (Table, Supplemental Digital Content 1, http://links.lww.com/INF/C820). Calendar year was significantly associated with CVS in univariate analyses ($P = 0.03$), but not in multivariate analysis ($P = 0.13$).

DISCUSSION

The ANRS-Pediacam cohort is one of the first studies designed to investigate the virologic response to ART initiated before 6 months of age in a resource-limited setting. The probability of VS lower than 400 copies/mL on at least 1 occasion (VS) was high [78.0% (66.0–79.0)]. But the probability of sustained virologic suppression within 6 months did not exceed 70%, regardless of the threshold used. Despite early treatment, the probability of death remained high, similar to that reported for a cohort of Ugandan HIV-infected infants.[19] These early deaths may reflect the rapid progression of disease in infants enrolled for medical care after severe immunodeficiency has set in.

Most studies have estimated VS rates in children from cross-sectional analyses of data for children currently followed-up at the clinical site,[11,17,23–29] leading to a potential overestimation of success, as patients lost to follow-up or dying after treatment initiation are not considered. One of the strengths of our study was prospective enrollment of infants from diagnosis with scheduled determinations of VL at 3-month intervals, making it possible to use survival models taking competing risks of death into account and to estimate the probability of maintaining VS for at least 6 months in infants.

The probability of achieving a VL <400 copies/mL at least once in Pediacam was similar to that reported in Uganda[19] and in Europe,[30] higher than that in a cohort of South African infants.[12]

TABLE 2. Factors Associated With Time to First Viral Load <1000 Copies (VS) in the First 2 Years of cART Begun Before the Age of 12 Months (ANRS-Pediacam Study, 2008–2013, Cameroon)

	Competing-Risks Regression in the Presence of Competing Death						
	Estimated Probability of VS			Univariate Analysis, N = 190		Multivariate Analysis, N = 167	
	N	n	%	Crude sHR (95% CI)	*P*	Adjusted sHR (95% CI)	*P*
Baseline characteristics							
Sex							
Male	83	65	80.0	1	0.74	—	—
Female	107	79	79.0	0.9 (0.7–1.3)		—	
Recruitment site							
HLD	40	30	80.0	1	0.47	1	0.33
CME/FCB	94	67	82.0	1.1 (0.7–1.7)		1.2 (0.8–1.9)	
CHE	56	47	85.0	1.3 (0.8–2.1)		1.4 (0.9–2.3)	
Age at cART initiation (months)							
<3	37	30	80.0	1	0.78	1	0.64
3–12	153	114	80.0	0.9 (0.6–1.4)		1.1 (0.7–1.6)	
Calendar year at cART initiation							
2010–2011	71	52	80.0	1	0.16	1	0.06
2008–2009	119	92	84.0	1.2 (0.9–1.7)		1.4 (0.9–2.0)	
Mode of inclusion							
At birth	60	48	83.0	1	0.28	1	0.84
After birth, but before 7 months of age	130	98	78.0	0.8 (0.6–1.2)		1.0 (0.7–1.6)	
Time from HIV diagnosis to cART initiation (weeks)							
≤2	132	82	75.0	1	0.98	—	—
2–6	51	31	75.0	1.0 (0.7–1.4)		—	
6–12*	7	—	—	—		—	
Father's HIV status							
HIV positive	45	34	79.0	1	0.59	—	—
HIV negative	43	36	83.0	1.1 (0.7–1.8)		—	
Unknown	102	74	79.0	0.9 (0.6–1.4)		—	
Mother receiving cART							
No	151	116	80.0	1	0.38	—	—
Yes	39	28	75.0	0.8 (0.6–1.2)		—	
Father receiving cART							
No	154	115	79.0	1	0.44	—	—
Yes	36	29	82.0	1.2 (0.8–1.7)		—	
Parents living with the infant							
Other relatives	24	17	64.0	1	0.12	1	0.31
Mother only	67	54	84.0	1.7 (1.0–2.8)		1.5 (0.9–2.6)	
Both parents	99	73	78.0	1.3 (0.8–2.1)		1.4 (0.8–2.3)	
Household size							
<5 people	90	70	81.0	1	0.75	—	—
5–8 people	65	48	78.0	0.9 (0.6–1.3)		—	
≥9 people	35	25	78.0	0.9 (0.6–1.3)		—	
Running water at home							
No	86	66	80.0	1	0.90	—	—
Yes	104	77	80.0	1. 0 (0.7–1.4)		—	
Electricity at home							
No	21	14	72.0	1	0.37	—	—
Yes	169	129	80.0	1. 3 (0.7–2.2)		—	
Functional fridge at home							
No	97	70	75.0	1	0.12	1	0.07
Yes	93	73	84.0	1. 3 (0.9–1.8)		1.3 (0.9–1.8)	
History of hospitalization or other medical events†							
No	48	38	85.0	1	0.66	—	—
Yes	132	106	83.0	0.9 (0.6–1.3)		—	
CD4 cell percentage							
<25.0%	113	87	81.0	1	0.33	—	—
≥25.0%	77	57	76.0	0.9 (0.6–1.2)		—	
Viral load in $\log_{10}$ copies/mL							
≥7.0	44	32	80.0	1.0	0.17	1	0.31
<7.0	146	114	85.0	1.2 (0.9–2.0)		1.2 (0.8–1.7)	
First cART regimen							
Lopinavir based	123	96	82.0	1	0.29	1	0.11
Nevirapine based	65	47	75.0	0.8 (0.6–1.2)		1.4 (0.9–2.3)	
Three nucleoside inhibitors*	2	—	—	—		—	
Prior exposure to nevirapine prophylaxis							
Yes	90	65	82.0	1	0.31	—	—
No	100	79	76.0	1.2 (0.8–1.6)		—	
Time-dependent characteristics							
Doses missed in the last 3 d, as reported by the carer							
≥1 missed dose	—	—	—	1	<0.01	1	<0.01
No missed dose	—	—	—	1.8 (1.4–2.3)		1.7 (1.3–2.3)	

cART indicates combined antiretroviral therapy; CI, confidence interval; CHE, Centre Hospitalier d'Essos; CME/FCB, Centre Mère et Enfant de la Fondation Chantal Biya; HLD, Hôpital Laquintinie de Douala; N, number of subjects; n, number of virologic successes in the variable category from cART initiation to month 24; %, estimated probability of virologic success; *P*, Wald test; sHR, subhazard ratio; VS, virologic success.

*Not included in the analysis.

†Convulsions, diarrhea or infectious disease.

Virologic response rates to ART in older children are generally higher than in infants in Africa and in Europe,[10,11,17,18,20–22,24,30–32] likely due to higher pretreatment plasma VL during infancy[17,32–35] and adherence entirely dependent on caregivers.[36]

In Pediacam, the only factor significantly associated with the achievement of VS was not having missed any drug doses in the 3 days before the visit. This marker of adherence was also associated with CVS and has been found associated with viral suppression in a study of young South African children.[20] The overall probability of missed dose over 2 years after ART exceeded 50% in our study, which highlights the difficulties faced by caregivers in maintaining daily adherence. Nevertheless, we previously showed that caregiver-reported missed doses does not have sufficient performance to replace VL measurement for identifying virologic failure.[37] Routine VL monitoring in pediatric cohorts is essential to optimize infant ART outcomes.

The lack of relation between VS and lopinavir/ritonavir-based regimen contrasts with the findings in previous trials performed in older children.[38,39] However, ritonavir-boosted lopinavir, available for young children, is an unpalatable liquid difficult to administer to infants,[40,41] potentially impairing its efficacy.

In conclusion, we showed that ART initiated in infancy is efficient in resource-limited settings since near 80% reach virologic suppression at least once within 2 years of treatment initiation. However, rates of success at least 6 months and early mortality remain unsatisfactory. The identification of good adherence as the major factor associated with VS, with no clear relationship to socioeconomic and environmental living conditions, suggests that the long-term daily administration of drugs to babies is difficult for caregivers. There is concern about the high risk of antiretroviral drug resistance mutations, particularly in infants initially treated with nevirapine-based regimens and not achieving VS within 2 years of treatment initiation, as demonstrated in previous studies.[42,43]

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