Scaling up antiretroviral therapy for HIV-infected children in Côte d'Ivoire: determinants of survival and loss to programme

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Objective To investigate deaths and losses to follow-up in a programme designed to scale up antiretroviral therapy (ART) for HIV-infected children in Côte d'Ivoire.

Methods Between 2004 and 2007, HIV-exposed children at 19 centres were offered free HIV serum tests (polymerase chain reaction tests in those aged < 18 months) and ART. Computerized monitoring was used to determine: (i) the number of confirmed HIV infections, (ii) losses to the programme (i.e. death or loss to follow-up) before ART, (iii) mortality and loss-to-programme rates during 12 months of ART, and (iv) determinants of mortality and losses to the programme.

Findings The analysis included 3876 ART-naïve children. Of the 1766 with HIV-1 infections (17% aged < 18 months), 124 (7.0%) died, 52 (2.9%) left the programme, 354 (20%) were lost to follow-up before ART, 259 (15%) remained in care without ART, and 977 (55%) started ART (median age: 63 months). The overall mortality rate during ART was significantly higher in the first 3 months than in months 4–12: 32.8 and 6.9 per 100 child-years of follow-up, respectively. Loss-to-programme rates were roughly double mortality rates and followed the same trend with duration of ART. Independent predictors of 12-month mortality on ART were pre-ART weight-for-age *z*-score < –2, percentage of CD4+ T lymphocytes < 10, World Health Organization HIV/AIDS clinical stage 3 or 4, and blood haemoglobin < 8 g/dl.

Conclusion The large-scale programme to scale up paediatric ART in Côte d'Ivoire was effective. However, ART was often given too late, and early mortality and losses to programme before and just after ART initiation were major problems.

Une traduction en français de ce résumé figure à la fin de l'article. *Al final del artículo se facilita una traducción al español.* الترجمة العربية لهذه الخلاصة في نهاية النص الكامل لهذه المقالة.

Introduction

In 2007, an estimated 2 million children and 13 million women of childbearing age worldwide were infected with HIV.[1] The HIV epidemic in children continues to grow, partly because only about 33% of HIV-infected pregnant women receive antiretroviral therapy (ART) for the prevention of mother-to-child transmission (PMTCT).[1]

The problems of caring for children with HIV differ from those in adults. First, over 50% of untreated HIV-infected children die before their second birthday.[2] Second, routine diagnosis of paediatric HIV infection is more difficult: definitive diagnosis in children aged < 18 months requires virological testing, which is often unavailable in resource-limited settings.[3] Moreover, clinicians must also take a dynamic view of HIV exposure among children because of the likelihood of infection during breastfeeding.[4] This need to take uninfected children into account is difficult to explain to parents. Third, providing a continuum of care covering postnatal diagnosis in infants and HIV treatment after a PMTCT intervention in mothers still remains a challenge in 2009.[1,5] Fourth, chronic diseases requiring lifelong daily treatment are more difficult to manage in children, especially when paediatric formulations and dosages are not available.[6,7] As a result of these difficulties, in 2008 only an estimated 38% of all children aged < 15 years worldwide thought to need ART actually received it.[8] Finally, additional issues, such as the need for informed consent, have led to a relative scarcity of studies on paediatric care in low-income countries and have put children at a disadvantage in AIDS research.[9–14] Increasing the availability of HIV care in developing countries provides an unprecedented challenge.[8] In particular, the public health impact of initiatives on paediatric HIV care in resource-limited settings must be assessed using conventional indicators of effectiveness.[15] The aims of this study were to investigate the effectiveness of a paediatric HIV treatment and care programme in Côte d'Ivoire, West Africa, over a 3-year period and to identify factors that influenced mortality and the number of children lost to the programme.

Methods

Setting and patient characteristics

In June 2004, Aconda, a nongovernmental organization created by researchers who had studied cohorts of HIV-infected adults and children in Abidjan, Côte d'Ivoire, between 1996 and 2003,[9,16] formed a partnership with the Institute of Public Health, Epidemiology and Development in Bordeaux, France, to study access to HIV care and treatment. The study was funded by the United States President's Emergency Plan for AIDS Relief through the Elizabeth Glaser Pediatric AIDS Foundation in Washington, DC, United States of America (USA).

Details of the Aconda programme have been described elsewhere.[17] Briefly, the Aconda team trained health workers in HIV care and implemented a standardized computer data management system which was controlled by a designated

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person in each study centre. Aconda staff visited study centres regularly and offered database management support online.

This analysis used data from children with HIV-1 infections, with or without concurrent HIV-2 infections, aged ≤ 15 years at 17 urban and 2 semi-urban health-care centres who had had at least one contact with the Aconda programme between 1 June 2004 and 30 November 2007. In 2008, the Aconda data management system evolved into a national HIV data management system for all Côte d'Ivoire under the auspices of the Ministry of Public Health.

Entry into the programme

The Aconda programme adopted a comprehensive family-based approach. Health-care workers were trained to offer HIV testing to every pregnant woman attending antenatal clinics and to encourage HIV-infected mothers to bring their children and partners with them for testing and counselling. Each pregnant woman with an HIV infection was immediately referred for an adult consultation. She then received PMTCT therapy, either a short regimen or ART depending on her clinical and immunological status, and underwent assessment at both antenatal and adult clinics.[18] Children aged ≤ 15 years entered the Aconda programme in one of two ways: (i) after referral for HIV testing at the age of ≥ 6 weeks because their mother had been diagnosed with HIV infection and had received PMTCT therapy, or (ii) after HIV testing at a paediatric clinic following presentation with AIDS-related symptoms, even if they had not been previously classified as exposed to or infected by HIV and even if their parents had not participated in the Aconda programme.

Standardized paediatric follow-up

The Aconda paediatric HIV care package included systematic paediatric HIV testing which varied according to the child's age. In those aged ≥ 18 months, the standard serum testing algorithm comprised a series of two rapid HIV assays: the Determine® HIV-1/2 assay (Inverness Medical, Bedford, United Kingdom of Great Britain and Northern Ireland) followed by the Genie II® HIV-1/HIV-2 assay (Bio-Rad laboratories, Marne-La-Coquette, France).[19] Children aged < 18 months were diagnosed virologically using a TaqMan HIV-1, ribonucleic acid (RNA), real-time polymerase chain reaction test (Hoffmann–La Roche, Basel, Switzerland) with a threshold of 300 copies/ml.[20] Children were regarded as having HIV-1 infections if, at any age, they tested positive for HIV-1 RNA in plasma at least once or if, at age ≥ 18 months, they were positive for HIV-1 on serum testing. Children who tested negative but who were still breastfeeding were defined as HIV-undetermined and were retested 2 months after the cessation of breastfeeding or at 18 months. A negative diagnosis was regarded as definite if it was made at least 2 months after the cessation of breastfeeding and children with this diagnosis were excluded from the programme.

All children with a confirmed HIV infection were seen monthly and had unrestricted free access to antiretroviral drugs and comprehensive care.[21] In all children, whether on ART or not, the CD4+ T lymphocyte (CD4 cell) count and CD4 cell percentage were measured every 6 months. Plasma viral load testing was not performed routinely after the diagnosis of HIV infection, even in children on ART. Pulmonary radiographs were available for children whose history and symptoms suggested tuberculosis.

Children initiated ART if they were either at World Health Organization (WHO) HIV/AIDS clinical stage 3 or 4 or at clinical stage 1 or 2 with impaired immunity (i.e. a CD4 cell percentage ≥ 25 at age < 12 months, ≥ 20 at 12–35 months or ≥ 15 at ≥ 36 months).[3] Until June 2007, first-line ART consisted of zidovudine or stavudine plus lamivudine plus nevirapine, efavirenz or nelfinavir. The drug combination used depended on the child's age, weight and blood haemoglobin level. Co-trimoxazole prophylaxis was given to all HIV-exposed children from the age of 6 weeks and to all HIV-infected children regardless of age, as recommended by national Ivorian guidelines.[21] A community-based women's organization provided psychological, social and nutritional support, advice on how to disclose test results, and adolescent and orphan care.

The Côte d'Ivoire National Programme paid for ART, co-trimoxazole prophylaxis, plasma HIV-1 RNA testing, HIV serum testing and CD4 cell counts for children aged < 15 years.[21] From April 2006, patients paid US$ 0.90 per prescription for each additional drug used against opportunistic infections. Patients received antiretroviral drugs and co-trimoxazole every month. A community-based team of experienced social workers and members of associations of people living with HIV/AIDS made telephone calls or home visits within 2 weeks to children who did not keep their scheduled appointments.[17]

Data management system

The national ethics committee of Côte d'Ivoire approved the Aconda data management system.[17] Standardized forms were used to record the following variables: (i) at the initial visit, date, sex, date of birth or age, height, weight, PMTCT history, breastfeeding status, haematology results and CD4 cell count and percentage; (ii) at each subsequent visit, date and weight; (iii) at ART initiation, date, WHO HIV/AIDS clinical stage and weight; (iv) date, name and quantity of drugs delivered for each prescription, whether or not for ART; (v) at each CD4 cell and blood cell count measurement, date, CD4 cell count, CD4 cell percentage, blood haemoglobin level, and blood platelet, granulocyte and leukocyte counts; and (vi) date of death or, for patients whose death had not been reported, the last date at which the patient was known to be alive.

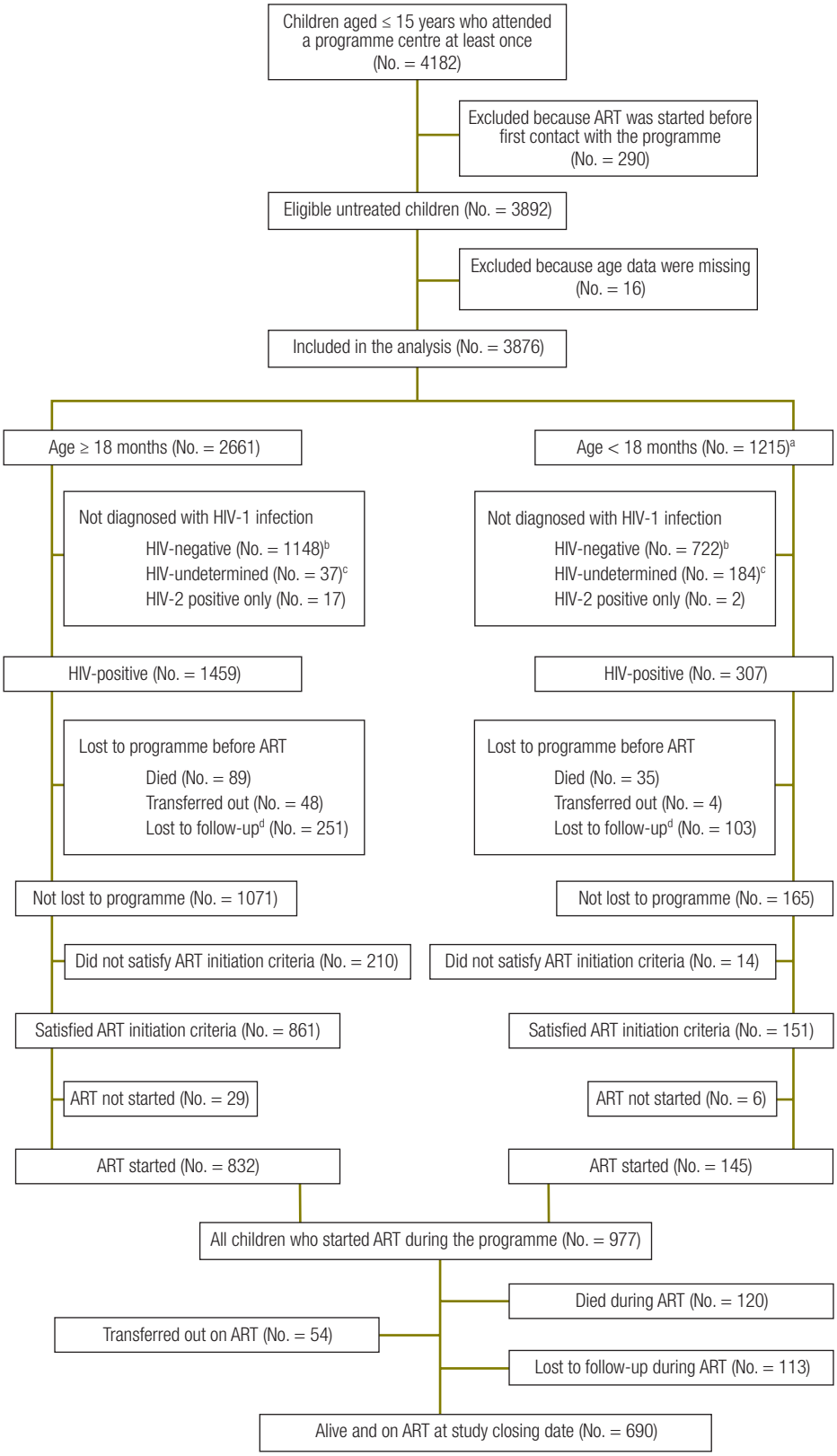
Statistical analysis

Kaplan–Meier analysis was used to determine the probability that a child aged < 18 months at first contact with the programme would be diagnosed with an HIV infection. We examined three outcomes for children with HIV-1 infection, with or without concurrent HIV-2 infection: death, loss-to-follow-up (i.e. last contact ≥ 3 months before 30 November 2007 if death had not been reported) and loss-to-programme (i.e. death or loss-to-follow-up).

Mortality and loss-to-programme rates, expressed in events per 100 child-years of follow-up, were calculated for the period between programme inclusion and ART initiation (i.e. the off-ART period), for the first 12 months on ART as a whole, and for months 0–3 and 4–12 of ART.

We estimated the probability that a death or loss-to-programme would occur during ART using the Kaplan–Meier method. We used crude and adjusted Cox proportional hazards regression models to identify baseline characteristics associated with death or a loss-to-programme during 12 months of ART. Characteristics considered included sex, haemoglobin

Fig. 1. **Flow diagram of the cohort enrolled in the Aconda HIV treatment programme for children, Côte d'Ivoire, 2004–2007**



ART, antiretroviral therapy; RNA, ribonucleic acid.

[a] Children aged < 18 months who were exposed to maternal HIV underwent virological testing (i.e. HIV-1 RNA measurement).

[b] HIV-negative children were excluded after complete cessation of breastfeeding.

[c] Children whose HIV status was undetermined were still being exposed to maternal HIV during breastfeeding at their last visit.

[d] Children were lost to follow-up if their last contact was more than 3 months before the end of the study.

Table 2. **Mortality and loss-to-programme rates in HIV-infected children before and after starting antiretroviral therapy (ART) in the Aconda HIV treatment programme, overall and by age group, Côte d'Ivoire, 2004–2007**

Category	Total children	Children who died	Lost to follow-up[a]	Follow-up (child-years)	Died (per 100 child-years)		Lost to programme[b] (per 100 child-years)	
	No.	No.	No.	No.	No.	95% CI	No.	95% CI
All children								
Off ART	1766	124	354	951	13.0	10.7–15.4	50.3	45.7–54.9
On ART								
Overall	977	107	80	741	14.4	11.7–17.2	25.2	21.6–28.9
0–3 months	977	71	44	217	32.8	25.0–40.5	53.1	43.2–63.0
4–12 months	829	36	36	524	6.9	4.6–9.2	13.7	10.5–17.0
Aged < 18 months								
Off ART	307	35	103	99	35.5	23.5–47.4	139.8	116.0–163.6
On ART								
Overall	145	19	22	91	20.9	11.3–30.5	45.1	31.0–59.2
0–3 months	145	13	16	30	43.7	19.5–68.0	97.5	61.3–133.7
4–12 months	109	6	6	61	9.8	1.8–17.8	19.6	8.3–30.9
Aged 18–59 months								
Off ART	586	43	126	352	12.2	8.5–15.9	48.0	40.6–55.3
On ART								
Overall	296	29	23	227	12.8	8.0–17.5	22.9	16.6–29.3
0–3 months	296	20	13	66	30.5	16.8–44.1	50.3	32.8–67.8
4–12 months	251	9	10	161	5.6	1.9–9.3	11.8	6.4–17.2
Aged ≥ 60 months								
Off ART	873	46	125	500	9.2	6.5–11.9	34.2	29.0–39.4
On ART								
Overall	536	59	35	423	13.9	10.3–17.6	22.2	17.6–26.8
0–3 months	536	38	15	121	31.3	21.2–41.5	43.7	31.7–55.7
4–12 months	469	21	20	302	7.0	3.9–10.0	13.6	9.3–17.8

ART, antiretroviral therapy; CI, confidence interval.
[a] Children were lost to follow-up if last contact was >3 months before the end of the study.
[b] Children were lost to the programme if they died or were lost to follow-up.

level, CD4 cell percentage, weight-for-age *z*-score, initial WHO HIV/AIDS clinical stage and initial ART regimen. Data were censored on 30 November 2007 for patients known to be alive at that date and, for those whose death had not been reported by that time, on the date of last contact with the care centre. Cox models took missing data into account. Analyses were carried out using SAS software, version 9.1 (SAS Institute Inc., Cary, NC, USA).

Results

In total, 4182 children attended a programme centre at least once. Of these, 290 (6.9%) were excluded from the analysis because they had started ART at first presentation and 16 (0.4%) were excluded because their age was unknown.

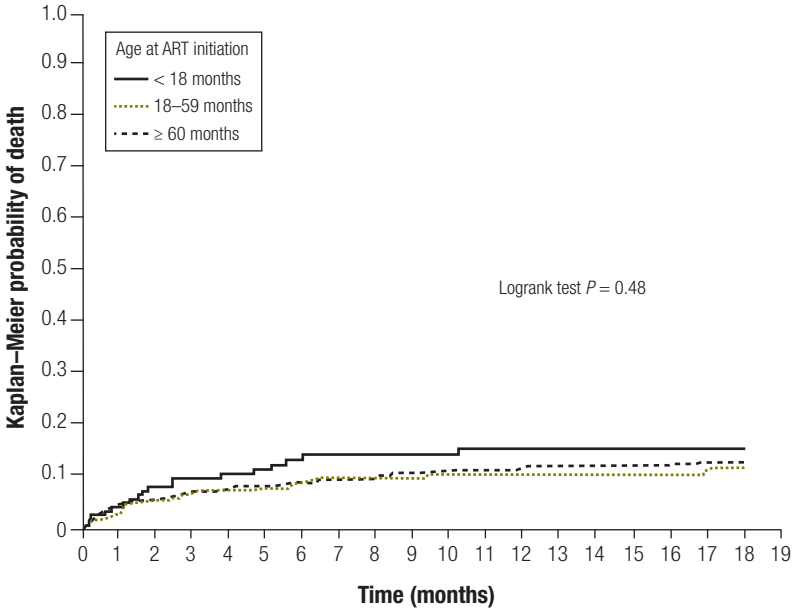
Fig. 1 provides details of the children who entered the programme, were tested for HIV, and received ART. Of the 3876 children included in the analysis, 1766 (46%) were diagnosed with an HIV-1 infection, with or without HIV-2, 19 (0.5%) were diagnosed with an HIV-2 infection only, 1870 (48%) tested negative for HIV and were excluded from the analysis, and 221 (5.7%) were classified as having an HIV-undetermined status at the end of the study period.

Among the 1215 children exposed to HIV and aged < 18 months at first presentation, the Kaplan–Meier probability of undergoing HIV RNA testing was 59% (95% confidence interval, CI: 56–63) at 1 month after the first contact with the programme, 76% (95% CI: 72–80) at 3 months and 80% (95% CI: 76–84) at 6 months. Of these 1215 children, 307 (25%) were confirmed as having an HIV infection at a median age of 9 months (interquartile range, IQR: 4–14), as shown in Fig. 1. The majority of children who did not undergo HIV RNA testing attended programme centres at the rural periphery of Abidjan. Only 413 (34%) children aged < 18 months had mothers who were involved in a PMTCT programme.

Of the 1766 children diagnosed with an HIV infection, 124 (7.0%) died without starting ART, 52 (2.9%) were transferred out of their programme centres, 354 (20%) were lost to follow-up before starting ART, 224 (13%) did not meet ART initiation criteria, 35 (2%) met ART initiation criteria but remained in care without starting ART, and 977 (55%) started ART before the end of the study.

Table 1 (available at: http://www.who.int/bulletin/volumes/88/7/09-068015) summarizes the demographic and clinical characteristics of children at diagnosis of HIV infection and at ART initiation. The median age of the 1766 children at diagnosis of HIV infection was 54 months. Of these children, 307 (17%) were aged < 18 months, 1378 (78%) underwent at least one CD4 cell measurement and 1142 (65%) were immediately eligible for ART: 374 (21%)

Fig. 2. **Kaplan–Meier probability of death during antiretroviral therapy (ART) in HIV-infected children in the Aconda HIV treatment programme, by age group, Côte d'Ivoire, 2004–2007**



ART, antiretroviral therapy.

on the basis of clinical criteria and 768 (44%) on immunological criteria. Overall, 977 children initiated ART a median of 1 month (IQR: 0–4) after inclusion in the Aconda programme.

Table 2 shows mortality and loss-to-programme rates for children who were and were not on ART. The mortality rate in all children who were off ART was 13.0 per 100 child-years of follow-up; in those aged < 18 months, 18–59 months and ≥ 60 months at first presentation, the rate was 35.5, 12.2 and 9.2 per 100 child-years, respectively (Table 2). In total, 478 (27%) children were lost to the programme before ART initiation, giving a loss-to-programme rate of 50.3 per 100 child-years of follow-up. The loss-to-programme rates before ART were 3 to 4 times higher than mortality rates for all age groups.

The 977 children who received ART had the following characteristics at the start of therapy: median age: 5 years; median weight-for-age *z*-score: −2.99; median CD4 cell percentage: 10.7; and proportions with a history of completed tuberculosis treatment: 2.7%; with active tuberculosis at baseline: 3.3%; in WHO HIV/AIDS clinical stage 3 or 4: 43%; on co-trimoxazole prophylaxis at ART initiation: 54%; and on co-trimoxazole prophylaxis within the first year following ART initiation: 89.5%. Sixty-five percent of patients, 66% of whom were aged ≥ 60 months, initiated ART with a combination of two nucleoside reverse transcriptase inhibitors, such as azidothymidine, stavudine, didanosine or lamivudine, and one non-nucleoside reverse transcriptase inhibitor, such as efavirenz or nevirapine. Overall, 33% of children initiated ART with a combination of two nucleoside reverse transcriptase inhibitors and one protease inhibitor, such as nelfinavir, though among those aged < 18 months, 55% started on a regimen containing a protease inhibitor (Table 1). The most frequent combinations prescribed were stavudine, lamivudine and efavirenz, in 28%, and azidothymidine, lamivudine and efavirenz, in 25%.

The overall mortality rate on ART was 14.4 per 100 child-years of follow-up and was significantly higher in the first 3 months of ART than during months 4–12, at 32.8 and 6.9 per 100 child-years of follow-up, respectively. Sixty-six percent of deaths during ART occurred within the first 3 months of therapy. During this period, the mortality rate was 43.7 per 100 child-years in children aged < 18 months and around 30 per 100 child-years in older children. Mortality rates decreased 4 to 6 times in all age groups after the third month on ART (Table 2). There was no significant difference in Kaplan–Meier probability of death during 12 months of ART between the age groups (logrank test $P = 0.48$) (Fig. 2 and Table 3).

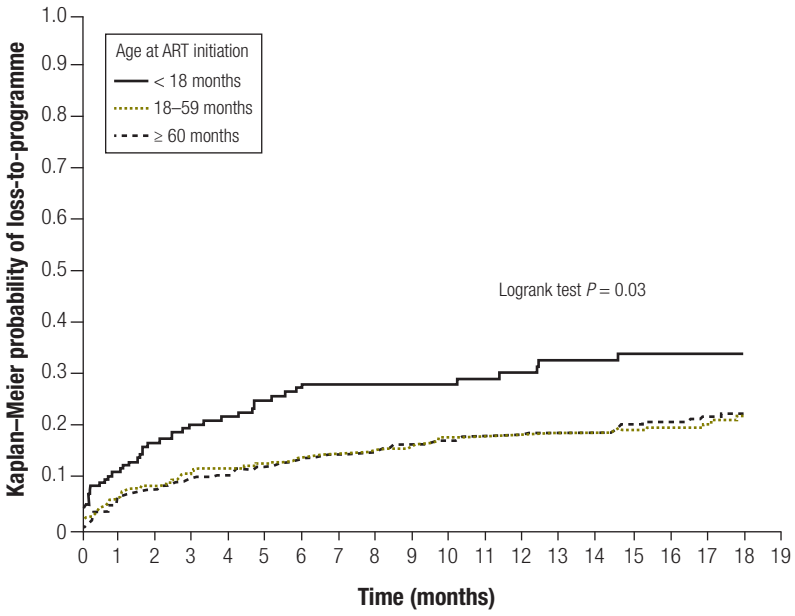
The loss-to-programme rate during ART was roughly double the mortality rate, both overall and in the different age groups (Table 2). It peaked at 53 per 100 child-years in the first 3 months of ART. The Kaplan–Meier probability of a child being lost to the programme 12 months after ART initiation was 0.30 in children aged < 18 months at ART initiation, 0.19 in those aged 18–59 months and 0.18 in those aged ≥ 60 months. The probability of a loss-to-programme differed

Table 3. **Kaplan–Meier probability of death during antiretroviral therapy (ART) in HIV-infected children in the Aconda HIV treatment programme, by age group, Côte d'Ivoire, 2004–2007**

Month of ART	Child age at ART initiation								
	< 18 months			18–59 months			≥ 60 months		
	Children at risk	Probability	95% CI	Children at risk	Probability	95% CI	Children at risk	Probability	95% CI
1	145	0.04	0.00–009	296	0.03	0.01–0.06	536	0.05	0.03–0.07
3	127	0.10	0.04–0.16	272	0.07	0.04–0.11	494	0.07	0.05–0.10
6	109	0.14	0.07–0.21	251	0.09	0.06–0.12	469	0.09	0.06–0.12
12	87	0.16	0.10–0.22	231	0.11	0.07–0.15	427	0.12	0.09–0.15
18	59	0.16	0.10–0.22	166	0.12	0.07–0.17	331	0.13	0.09–0.17

ART, antiretroviral therapy; CI, confidence interval.

Fig. 3. **Kaplan–Meier probability of loss-to-programme[a] during antiretroviral therapy (ART) in HIV-infected children in the Aconda HIV treatment programme, by age group, Côte d'Ivoire, 2004–2007**



ART, antiretroviral therapy.

[a] Children were lost to the programme if they died or were lost to follow-up (i.e. their last contact was > 3 months before the end of the study).

significantly between the age groups on univariate analysis (logrank test $P = 0.03$) (Fig. 3 and Table 4).

Data on demographic and clinical variables of interest were recorded for 746 (76%) of the 977 children who received ART. Associations between these variables and mortality and loss-to-programme during ART were identified using Cox proportional hazards regression models. It was found that both mortality and loss-to-programme were independently and significantly associated with a weight-for-age-*z*-score < −2, a CD4 cell percentage < 10 and WHO HIV/AIDS clinical stage 3 or 4 (Table 5). A blood haemoglobin level < 8 g/dl was significantly associated with mortality alone. There was neither significant association between any pre-ART variable and the adjusted risk of mortality or loss-to-programme, nor between age, sex, co-trimoxazole prophylaxis at baseline or initial ART regimen and outcomes. Stratifying the data by age group gave similar results.

Discussion

The results of our study revealed information important for guiding the expansion of paediatric HIV care. First, 86% of children in the programme who were eligible for ART according to WHO 2006 criteria started therapy. Second, although over 75% of those aged < 18 months had an HIV-RNA test, many were tested ≥ 3 months after first contact with the programme, which meant that HIV diagnosis and ART were too late.[22] Third, although the percentage of children who received co-trimoxazole in the programme (i.e. 50% of those off ART and 90% of those on ART) did not meet guideline recommendations,[23] useful information has been collected for sub-Saharan Africa, where data are generally lacking.[22,24] Fourth, mortality rates after the first 3 months of ART in all age groups were consistently lower than before therapy or during the first 3 months, despite children being relatively old at ART initiation and often being severely immunocompromised. Loss-to-programme rates were twice as high but followed similar trends in all age groups.

Other studies have shown that paediatric responses to ART are similar in low- and high-income countries but that, in low-income countries, therapy is often started too late, when children are already immunodeficient.[9,10,12,13,25–28] This also occurred in our cohort and most likely resulted in high rates of mortality and loss to follow-up, with the latter often including underdocumented mortality.

To improve the accessibility and effectiveness of HIV care in Côte d'Ivoire, several systematic weaknesses must be addressed. First, strengthening the links between PMTCT services and paediatric HIV care could improve prognosis in children who still acquire HIV infections. Second, survival on ART has been

Table 4. **Kaplan–Meier probability of loss-to-programme[a] during antiretroviral therapy (ART) in HIV-infected children in the Aconda HIV treatment programme, by age group, Côte d'Ivoire, 2004–2007**

Month of ART	Child age at ART initiation								
	< 18 months			18–59 months			≥ 60 months		
	Children at risk	Probability	95% CI	Children at risk	Probability	95% CI	Children at risk	Probability	95% CI
1	145	0.11	0.05–0.17	296	0.06	0.03–0.09	536	0.06	0.03–0.10
3	127	0.20	0.13–0.27	272	0.11	0.07–0.16	494	0.10	0.07–0.13
6	109	0.28	0.20–0.36	252	0.14	0.10–0.18	469	0.14	0.10–0.18
12	87	0.30	0.21–0.39	231	0.19	0.14–0.24	427	0.18	0.14–0.22
18	59	0.34	0.25–0.43	166	0.22	0.17–0.27	331	0.23	0.19–0.27

ART, antiretroviral therapy; CI, confidence interval.

[a] Children were lost to the programme if they died or were lost to follow-up (i.e. last contact was > 3 months before the end of the study).

Table 5. **Factors associated with mortality and loss to programme[a] during 12 months of antiretroviral therapy (ART) in 746 HIV-infected children in the Aconda HIV treatment programme, as per Cox proportional hazards regression models, Côte d'Ivoire, 2004–2007**

Pre-ART characteristics	12-month mortality (92 events)					12-month loss-to-programme (153 events)				
	No.	Crude HR	95% CI	Adjusted HR	95% CI	No.	Crude HR	95% CI	Adjusted HR	95% CI
Age category (months)										
<18	114	0.93	0.51–1.68	1.08	0.55–2.10	114	1.17	0.76–1.81	1.32	0.80–2.17
18–59	230	0.67	0.40–1.10	0.92	0.53–1.57	203	0.76	0.52–1.12	0.97	0.64–1.47
≥60	402		Reference			402		Reference		
Sex										
Male	395		Reference.			395		Reference		
Female	351	1.02	0.67–1.54	1.01	0.66–1.53	351	0.91	0.66–1.26	0.94	0.68–1.31
CD4 cell percentage										
<10	324	2.96	1.88–4.55	2.68	1.67–4.27	324	1.98	1.43–2.73	1.75	1.24–2.48
≥10 or unknown	422		Reference			422		Reference		
Blood haemoglobin (g/dl)										
<8 or unknown	235	1.71	1.13–2.59	1.87	1.21–2.84	235	1.20	0.85–1.68	1.22	0.86–1.72
≥8	511		Reference			511		Reference		
Weight-for-age *z*-score										
≤–2	522	4.31	2.16–8.58	3.50	1.74–7.02	522	2.52	1.63–3.90	2.19	1.41–3.42
>–2	224		Reference			224		Reference		
WHO HIV/AIDS clinical stage										
1–2	293		Reference			293		Reference		
3–4 or unknown	453	2.72	1.63–4.50	2.08	1.24–3.50	453	2.23	1.54–3.24	1.97	1.34–2.87
Co-trimoxazole prophylaxis at baseline										
No	261		Reference			261		Reference		
Yes	485	0.89	0.58–1.38	0.99	0.64–1.54	485	0.73	0.52–1.01	0.76	0.54–1.06
Initial ART regimen										
NNRTI-based	528		Reference			528		Reference		
PI-based	202	0.88	0.54–1.42	1.01	0.59–1.72	202	0.97	0.67–1.39	1.02	0.68–1.52
Other regimen	16	1.53	0.48–4.86	1.18	0.35–3.93	16	0.92	0.29–2.92	0.66	0.20–2.16

ART, antiretroviral therapy; CD4, CD4+ T lymphocyte; CI, confidence interval; HR, hazard ratio; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; Ref., reference category.

[a] Children were lost to the programme if they died or were lost to follow-up (i.e. last contact was >3 months before the end of the study).

associated with a low baseline CD4 cell count in both resource-rich[29,30] and low-income countries.[9,10,12,13] Earlier access to treatment could prevent many deaths.[28] The significant drop in mortality during ART we observed after 3 months has been reported elsewhere in Africa.[13,31] The early peak in mortality may have been due to severe malnutrition, ART toxicity or immune reconstitution inflammatory syndrome (IRIS), which may be common in young children with a low CD4 cell count at ART initiation, especially if therapy is started too late. Indeed, IRIS has been associated with high morbidity in South Africa[32] and Thailand.[33] Our findings support the WHO 2008 recommendation that ART should be started immediately in all HIV-infected infants.[34]

A third systematic weakness in Africa is the limited availability of HIV-RNA tests for infants. Tests should be offered to HIV-exposed infants as early as possible after the age of 6 weeks and should be repeated if children are still exposed via breastfeeding. The routine use of dried blood spot testing could help increase early HIV diagnosis in infants aged over 6 weeks.[35,36] Fourth, severe malnutrition remains the most important predictor of both mortality and loss-to-programme, even compared with a low CD4 cell count. However, impaired immune status is generally an even stronger predictor among HIV-infected children off ART.[37] Finally, although our findings on mortality are encouraging, mortality rates would double if we assumed that losses to the programme may be due to undocumented deaths, as observed in adult HIV studies.[38,39]

Overall, our paediatric ART cohort encountered the same operational problems observed in adult ART programmes: an early peak in mortality on ART and high cohort attrition when programmes are scaled-up.[40–42] Socioeconomic factors are among the primary reasons for losses to follow-up.[43] New strategies are urgently needed to retain children and their caretakers in HIV programmes.

In this study, we showed that clinical markers, such as weight-for-age, haemoglobin level and CD4 cell count, can help predict responses to ART in low-income countries. Data on these markers are easy to collect and could provide information for improving paediatric HIV care and assessing programmes.

Finally, the successful and rapid implementation of paediatric ART programmes depends on dealing urgently with several programmatic issues. An effort should be made to identify all HIV-infected infants early. The barriers to scaling-up treatment include the failure to identify maternal HIV infection, weak links between PMTCT and child care programmes, and limited access to HIV-RNA testing for early diagnosis.[5,7,44] Education about ART should start antenatally and should be monitored to increase postnatal infant HIV screening from the age of 6 weeks. Political commitment is needed to mobilize health-care and community leaders. Lastly, ensuring an adequate number of trained staff is essential for the successful scaling-up ART in this context.[45] ■

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مخلص

توسيع مجال المعالجة بمضادات الفيروسات للأطفال المصابين بفيروس العوز المناعي البشري في ساحل العاج: محددات البقاء على قيد الحياة والخسائر في البرنامج

الغرض تقصي الوفيات والخسائر التالية لبرنامج معد بغرض تعميم المعالجة بمضادات الفيروسات للأطفال المصابين بفيروس الإيدز في ساحل العاج.

الطريقة خلال الفترة من 2004 حتى 2007، قُدمَ مجانياً للأطفال المعرضين لفيروس الإيدز في 19 مركزاً اختبارات مصلية للفيروس (اختبارات تفاعل البوليميراز السلسلي لمن هم أقل من عمر 18 شهراً) وعلاجٌ بمضادات الفيروسات القهقرية. واستخدم الرصد المحوسب لتحديد: (ا) عدد العداوى المؤكدة بالفيروس، (ب) خسائر البرنامج (مثل الوفيات أو فقدان المتابعة في البرنامج) قبل المعالجة بمضادات الفيروسات القهقرية، (ج) معدلات الوفيات وخسائر البرنامج خلال 12 شهراً من المعالجة بمضادات الفيروسات القهقرية، (د) محددات الوفيات والخسائر في البرنامج.

الموجودات اشتمل التحليل على 3876 طفلاً لم يعالجوا من قبل بمضادات الفيروسات القهقرية. ومن بين 1766 طفلاً تبين إصابتهم بعدوى فيروس العوز المناعي البشري من النمط 1- (17% منهم أقل من عمر 18 شهراً)، توفي 124 طفلاً (7.0%)، وترك 52 طفلاً البرنامج (2.9%)، وفُقدَ 354 (20%) طفلاً من المتابعة قبل بدء المعالجة بمضادات الفيروسات القهقرية، وظل 259 طفلاً (15%) يخضعون للرعاية بدون معالجة بمضادات الفيروسات القهقرية، وبدأ 977 طفلاً (55%) المعالجة بمضادات الفيروسات القهقرية (وسيط العمر: 63 شهراً). وكان إجمالي معدل الوفيات أثناء المعالجة بمضادات الفيروسات القهقرية أعلى بدرجة يُعتَد بها خلال الشهور الثلاثة الأولى مقارنة بالشهور من 4 حتى 12 شهراً من المعالجة: حيث كان المعدلان بالترتيب 32.8 و 6.9 لكل 100 طفل بالنسبة لسنوات المتابعة. وبلغت معدلات خسائر متابعة البرنامج ضعف معدلات الوفيات تقريباً، واتبعت نفس النزعة بالنسبة لمدة المعالجة بمضادات الفيروسات القهقرية. والمونبئات المستقلة للوفيات طوال 12شهراً من المعالجة بمضادات الفيروسات القهقرية كانت هي الوزن مقابل العمر قبل بدء المعالجة بمضادات الفيروسات القهقرية للحرز z أقل من 2 -، ونسبة خلايا الليمفاويات التائية +CD4 أقل من 10، والمرحلتان الإكلينيكيتان 3 أو 4 للإيدز والعدوى بفيروسه بحسب تصنيف منظمة الصحة العالمية، وهيموغلوبين الدم أقل من 8 غرام لكل ديسيلتر.

الاستنتاج كان البرنامج الموسع لتعميم معالجة الأطفال بمضادات الفيروسات القهقرية في ساحل العاج فعالاً. إلا أن المعالجة بمضادات الفيروسات القهقرية غالباً ما كانت تُعطى متأخرة جداً، وكانت الوفيات والخسائر المبكرة في البرنامج قبل بدء المعالجة بمضادات الفيروسات القهقرية أو فور بدئها هي المشاكل الكبرى.

Résumé

Élargissement du traitement antirétroviral pour les enfants infectés par le VIH en Côte d'Ivoire : déterminants de la survie et des pertes pour le programme

Objectif Étudier la mortalité et le nombre de perdus de vue dans le cadre d'un programme conçu pour étendre le traitement antirétroviral (ART) des enfants infectés par le VIH en Côte d'Ivoire.

Méthodes Entre 2004 et 2007, on a proposé gratuitement, dans 19 centres, à l'intention des enfants exposés au VIH, un dépistage sérologique de ce virus (un test d'amplification génique pour les moins de 18 mois) et un traitement ART. On a fait appel à un suivi informatisé pour déterminer : (i) le nombre d'infections à VIH confirmées, (ii) les pertes pour le programme (c'est-à-dire les morts et les perdus de vue) avant l'administration du traitement ART, (iii) la mortalité et les taux de perte pour le programme au cours des 12 mois de traitement ART, et (iv) les déterminants de la mortalité et des pertes pour le programme.

Résultats L'analyse a porté sur 3876 enfants encore jamais traités par des antirétroviraux. Parmi les 1766 enfants atteints d'une infection à VIH-1 (dont 17 % de moins de 18 mois), 124 (7,0 %) sont décédés, 52 (2,9 %) ont quitté le programme, 354 (20 %) ont été perdus de vue avant la mise en route du traitement ART, 259 (15 %) ont continué de recevoir des soins sans prendre d'ARV et 977 (55 %) ont débuté un traitement ART (âge médian : 63 mois). Le taux de mortalité global au cours du

traitement était significativement plus élevé pendant les 3 premiers mois qu'au cours des mois 4 à 12, soit 32,8 et 6,9 décès pour 100 enfants-années de suivi, respectivement. Les taux de perte pour le programme atteignaient approximativement le double des taux de mortalité et suivaient les mêmes tendances avec la durée du traitement. Les facteurs prédictifs indépendants de la mortalité à 12 mois sous ART étaient : rapport poids/âge avant le traitement en z-score < -2, pourcentage de lymphocytes T CD4+ < 10, stade clinique du VIH/sida selon l'Organisation mondiale de la Santé 3 ou 4 et taux d'hémoglobine < 8 g/dl.

Conclusion Le programme à grande échelle pour étendre le traitement ART pédiatrique en Côte d'Ivoire s'est révélé efficace. Néanmoins, ce traitement était souvent administré trop tard. La mortalité précoce et les pertes pour le programme avant et juste après la mise en route du traitement constituaient des problèmes majeurs.

Resumen

Expansión del tratamiento antirretroviral entre niños infectados por el VIH en Côte d'Ivoire: determinantes de la supervivencia y de las pérdidas de seguimiento

Objetivo Investigar las defunciones y las pérdidas de seguimiento en un programa concebido para extender masivamente el tratamiento antirretroviral (TAR) entre niños infectados por el VIH en Côte d'Ivoire.

Métodos Entre 2004 y 2007, en 19 centros se ofreció a los niños expuestos al VIH pruebas gratuitas del VIH en suero (reacción en cadena de la polimerasa para menores de 18 meses) y TAR. Se instauró un sistema de vigilancia computadorizada para determinar: (i) el número de infecciones confirmadas por el VIH, (ii) las bajas del programa (es decir, las defunciones o las pérdidas de seguimiento) antes del TAR, (iii) las tasas de mortalidad y de pérdida de seguimiento durante 12 meses de TAR, y (iv) los determinantes de la mortalidad y las pérdidas de seguimiento.

Resultados El análisis abarcó a 3876 niños no sometidos anteriormente a TAR. De los 1766 con infección por VIH-1 (17% menores de 18 meses), 124 (7,0%) murieron, 52 (2,9%) abandonaron el programa, 354 (20%) se perdieron durante el seguimiento antes del TAR, 259 (15 %) siguieron atendidos sin TAR, y 977 (55%) comenzaron el TAR (mediana de la edad: 63 meses). La tasa de mortalidad global durante el TAR fue significativamente mayor en los tres primeros meses que en los meses 4 a 12: 32,8 y 6,9 por 100 niños-año de seguimiento, respectivamente. Las tasas de pérdida de seguimiento fueron aproximadamente el doble de las tasas de mortalidad y siguieron la misma tendencia con la duración de la TAR. Los factores predictivos independientes de la mortalidad a 12 meses entre los sometidos a TAR fueron un valor < –2 del estadístico *Z* del peso para la edad antes del TAR, un porcentaje de linfocitos T CD4+ < 10, la fase clínica 3 o 4 del VIH/sida según definición de la OMS, y una hemoglobinemia < 8 g/dl.

Conclusión El programa a gran escala implantado para extender masivamente el TAR pediátrico en Côte d'Ivoire fue eficaz. Sin embargo, dicha terapia se instauró a menudo demasiado tarde, y los principales problemas fueron la mortalidad temprana y las pérdidas de seguimiento antes e inmediatamente después del inicio del TAR.

References

1. United Nations Programme for HIV/AIDS. *2008 report on the global AIDS epidemic*. Geneva: UNAIDS; 2008.
2. Newell ML, Coovadia H, Cortina-Borja M, Rollins N, Gaillard P, Dabis F; Ghent International AIDS Society (IAS) Working Group on HIV Infection in Women and Children. Mortality of infected and uninfected infants born to HIV-infected mothers in Africa: a pooled analysis. *Lancet* 2004;364:1236–43. doi:10.1016/S0140-6736(04)17140-7 PMID:15464184
3. *WHO HIV prevention and treatment guidelines. Antiretroviral therapy of HIV infection in infants and children in resource-limited settings, towards universal access: recommendations for a public health approach (2006 version).* Geneva: World Health Organization; 2006.
4. Coutsoudis A, Dabis F, Fawzi W, Gaillard P, Haverkamp G, Harris DR et al.; Breastfeeding and HIV International Transmission Study Group. Late postnatal transmission of HIV-1 in breast-fed children: an individual patient data meta-analysis. *J Infect Dis* 2004;189:2154–66. doi:10.1086/420834 PMID:15181561
5. Tonwe-Gold B, Ekouevi DK, Bosse CA, Toure S, Koné M, Becquet R et al. Implementing family-focused HIV care and treatment: the first 2 years' experience of the mother-to-child transmission-plus program in Abidjan, Côte d'Ivoire. *Trop Med Int Health* 2009;14:204–12. doi:10.1111/j.1365-3156.2008.02182.x PMID:19236666
6. De Baets AJ, Bulterys M, Abrams EJ, Kankassa C, Pazvakavambwa IE. Care and treatment of HIV-infected children in Africa: issues and challenges at the district hospital level. *Pediatr Infect Dis J* 2007;26:163–73. doi:10.1097/01.inf.0000253040.82669.22 PMID:17259881
7. Orne-Gliemann J, Becquet R, Ekouevi DK, Leroy V, Perez F, Dabis F. Children and HIV/AIDS: from research to policy and action in resource-limited settings. *AIDS* 2008;22:797–805. doi:10.1097/QAD.0b013e3282f4f45a PMID:18427197
8. *Towards universal access. Scaling up priority HIV/AIDS interventions in the health sector. Progress report 2009.* Geneva: World Health Organization, United Nations Programme for HIV/AIDS, United Nations Children's Fund; 2009. Available from: http://www.who.int/hiv/pub/tuapr_2009_en.pdf [accessed 10 December 2009].
9. Fassinou P, Elenga N, Rouet F, Laguide R, Kouakoussui KA, Timite M et al. Highly active antiretroviral therapies among HIV-1-infected children in Abidjan, Côte d'Ivoire. *AIDS* 2004;18:1905–13. doi:10.1097/00002030-200409240-00006 PMID:15353976
10. Puthanakit T, Oberdorfer A, Akarathum N, Kanjanavanit S, Wannarit P, Sirisanthana T et al. Efficacy of highly active antiretroviral therapy in HIV-infected children participating in Thailand's National Access to Antiretroviral Program. *Clin Infect Dis* 2005;41:100–7. doi:10.1086/430714 PMID:15937769
11. Chiappini E, Galli L, Tovo PA, Gabiano C, Gattinara GC, Guarino A et al.; Italian Register for HIV Infection in Children. Virologic, immunologic, and clinical benefits from early combined antiretroviral therapy in infants with perinatal HIV-1 infection. *AIDS* 2006;20:207–15. doi:10.1097/01.aids.0000200529.64113.3e PMID:16511413
12. O'Brien DP, Sauvageot D, Zachariah R, Humblet P; Medecins Sans Frontieres. In resource-limited settings good early outcomes can be achieved in children using adult fixed-dose combination antiretroviral therapy. *AIDS* 2006;20:1955–60. doi:10.1097/01.aids.0000247117.66585.ce PMID:16988517
13. Bolton-Moore C, Mubiana-Mbewe M, Cantrell RA, Chintu N, Stringer EM, Chi BH et al. Clinical outcomes and CD4 cell response in children receiving antiretroviral therapy at primary health care facilities in Zambia. *JAMA* 2007;298:1888–99. doi:10.1001/jama.298.16.1888 PMID:17954540

14. Sutcliffe CG, van Dijk JH, Bolton C, Persaud D, Moss WJ. Effectiveness of antiretroviral therapy among HIV-infected children in sub-Saharan Africa. *Lancet Infect Dis* 2008;8:477–89. doi:10.1016/S1473-3099(08)70180-4 PMID:18652994
15. Rabkin M, El-Sadr W, De Cock K; the Bellagio HIV/Health Systems Working Group. The impact of scale-up on health systems: a priority research agenda. *J Acquir Immune Defic Syndr* 2009;52(Suppl 1):S6–11. PMID:19858943
16. Anglaret X, Messou E, Ouassa T, Toure S, Dakoury-Dogbo N, Combe P et al.; ANRS 1203 Study Group. Pattern of bacterial diseases in a cohort of HIV-1 infected adults receiving cotrimoxazole prophylaxis in Abidjan, Côte d'Ivoire. *AIDS* 2003;17:575–84. doi:10.1097/00002030-200303070-00013 PMID:12598778
17. Toure S, Kouadio B, Seyler C, Traore M, Dakoury-Dogbo N, Duvignac J et al.; Aconda Study Group. Rapid scaling-up of antiretroviral therapy in 10,000 adults in Côte d'Ivoire: 2-year outcomes and determinants. *AIDS* 2008;22:873–82. doi:10.1097/QAD.0b013e3282f768f8 PMID:18427206
18. *WHO HIV prevention and treatment guidelines. Antiretroviral drugs for treating pregnant women and preventing HIV infection in infants, towards universal access: recommendations for a public health approach.* Geneva: World Health Organization; 2006.
19. Rouet F, Ekouevi DK, Inwoley A, Chaix ML, Burgard M, Bequet L et al. Field evaluation of a rapid human immunodeficiency virus (HIV) serial serologic testing algorithm for diagnosis and differentiation of HIV type 1 (HIV-1), HIV-2, and dual HIV-1-HIV-2 infections in West African pregnant women. *J Clin Microbiol* 2004;42:4147–53. doi:10.1128/JCM.42.9.4147-4153.2004 PMID:15365003
20. Rouet F, Ekouevi DK, Chaix ML, Burgard M, Inwoley A, Tony TD et al. Transfer and evaluation of an automated, low-cost real-time reverse transcription-PCR test for diagnosis and monitoring of human immunodeficiency virus type 1 infection in a West African resource-limited setting. *J Clin Microbiol* 2005;43:2709–17. doi:10.1128/JCM.43.6.2709-2717.2005 PMID:15956387
21. de Côte d'Ivoire R. *Guide de prise en charge pédiatrique de l'infection par le VIH en Côte d'Ivoire*. Abidjan: Ministère de la Santé et de l'Hygiène Publique, Ministère de la Lutte contre le SIDA; 2006. French.
22. Harambat J, Fassinou P, Becquet R, Touré P, Rouet F, Dabis F et al.; ANRS 1201/1202 Ditrame Plus Study Group. 18-month occurrence of severe events among early diagnosed HIV-infected children before antiretroviral therapy in Abidjan, Côte d'Ivoire: a cohort study. *BMC Public Health* 2008;8:169. doi:10.1186/1471-2458-8-169 PMID:18492259
23. *WHO HIV prevention and treatment guidelines. Guidelines for co-trimoxazole prophylaxis for HIV-related infections in children, adults and adolescents in resource-limited settings: recommendations for a public health approach.* Geneva: World Health Organization; 2006.
24. Zachariah R, Harries AD, Luo C, Bachman G, Graham SM. Scaling-up co-trimoxazole prophylaxis in HIV-exposed and HIV-infected children in high HIV-prevalence countries. *Lancet Infect Dis* 2007;7:686–93. doi:10.1016/S1473-3099(07)70239-6 PMID:17897611
25. Rouet F, Fassinou P, Inwoley A, Anaky MF, Kouakoussui A, Rouzioux C et al.; ANRS 1244/1278 Programme Enfants Yopougon. Long-term survival and immuno-virological response of African HIV-1-infected children to highly active antiretroviral therapy regimens. *AIDS* 2006;20:2315–9. doi:10.1097/QAD.0b013e328010943b PMID:17117017
26. Wamalwa DC, Farquhar C, Obimbo EM, Selig S, Mbori-Ngacha DA, Richardson BA et al. Early response to highly active antiretroviral therapy in HIV-1-infected Kenyan children. *J Acquir Immune Defic Syndr* 2007;45:311–7. PMID:17356470
27. Reddi A, Leeper SC, Grobler AC, Geddes R, France KH, Dorse GL et al. Preliminary outcomes of a paediatric highly active antiretroviral therapy cohort from KwaZulu-Natal, South Africa. *BMC Pediatr* 2007;7:13. doi:10.1186/1471-2431-7-13 PMID:17367540
28. Violari A, Cotton MF, Gibb DM, Babiker AG, Steyn J, Madhi SA et al.; CHER Study Team. Early antiretroviral therapy and mortality among HIV-infected infants. *N Engl J Med* 2008;359:2233–44. doi:10.1056/NEJMoa0800971 PMID:19020325
29. Newell ML, Patel D, Goetghebuer T, Thorne C; European Collaborative Study. CD4 cell response to antiretroviral therapy in children with vertically acquired HIV infection: is it associated with age at initiation? *J Infect Dis* 2006;193:954–62. doi:10.1086/500842 PMID:16518757
30. Faye A, Le Chenadec J, Dollfus C, Thuret I, Douard D, Firtion G et al.; French Perinatal Study Group. Early versus deferred antiretroviral multidrug therapy in infants infected with HIV type 1. *Clin Infect Dis* 2004;39:1692–8. doi:10.1086/425739 PMID:15578372
31. KIDS-ART-LINC Collaboration. Low risk of death, but substantial program attrition, in pediatric HIV treatment cohorts in Sub-Saharan Africa. *J Acquir Immune Defic Syndr* 2008;49:523–31. doi:10.1097/QAI.0b013e31818aadce PMID:18989227
32. Smith K, Kuhn L, Coovadia A, Meyers T, Marais BJ, Barry G, et al. Immune reconstitution inflammatory syndrome in HIV-infected infants and young children initiating ART (abstract 75). In: *Fifteenth Conference on Retroviruses and Opportunistic Infections, Boston, 3–6 February 2008.*
33. Puthanakit T, Oberdorfer P, Akarathum N, Wannarit P, Sirisanthana T, Sirisanthana V. Immune reconstitution syndrome after highly active antiretroviral therapy in human immunodeficiency virus-infected thai children. *Pediatr Infect Dis J* 2006;25:53–8. doi:10.1097/01.inf.0000195618.55453.9a PMID:16395104
34. Report of the WHO Technical Reference Group. *Paediatric HIV/ART Care Guideline Group meeting: revised treatment recommendations for infants.* Geneva: World Health Organization; 2008.
35. Sherman GG, Stevens G, Jones SA, Horsfield P, Stevens WS. Dried blood spots improve access to HIV diagnosis and care for infants in low-resource settings. *J Acquir Immune Defic Syndr* 2005;38:615–7. doi:10.1097/01.qai.0000143604.71857.5d PMID:15793374
36. Creek T, Tanuri A, Smith M, Seipone K, Smit M, Legwaila K et al. Early diagnosis of human immunodeficiency virus in infants using polymerase chain reaction on dried blood spots in Botswana's national program for prevention of mother-to-child transmission. *Pediatr Infect Dis J* 2008;27:22–6. doi:10.1097/INF.0b013e3181469050 PMID:18162933
37. Cross Continents Collaboration for Kids (3Cs4kids) Analysis and Writing Committee. Markers for predicting mortality in untreated HIV-infected children in resource-limited settings: a meta-analysis. *AIDS* 2008;22:97–105. doi:10.1097/01.aids.0000302262.51286.a5 PMID:18090397
38. Anglaret X, Toure S, Gourvellec G, Tchehy A, Zio L, Zaho M et al. Impact of vital status investigation procedures on estimates of survival in cohorts of HIV-infected patients from Sub-Saharan Africa. *J Acquir Immune Defic Syndr* 2004;35:320–3. doi:10.1097/00126334-200403010-00015 PMID:15076249
39. Yu JK, Chen SC, Wang KY, Chang CS, Makombe SD, Schouten EJ et al. True outcomes for patients on antiretroviral therapy who are "lost to follow-up" in Malawi. *Bull World Health Organ* 2007;85:550–4. doi:10.2471/BLT.06.037739 PMID:17768504
40. Brinkhof MW, Dabis F, Myer L, Bangsberg DR, Boulle A, Nash D et al.; ART-LINC, IeDEA. Early loss of HIV-infected patients on potent antiretroviral therapy programmes in lower-income countries. *Bull World Health Organ* 2008;86:559–67. doi:10.2471/BLT.07.044248 PMID:18670668
41. Brinkhof MW, Pujades-Rodriguez M, Egger M, Emery S. Mortality of patients lost to follow-up in antiretroviral treatment programmes in resource-limited settings: systematic review and meta-analysis. *PLoS ONE* 2009;4:e5790. doi:10.1371/journal.pone.0005790 PMID:19495419
42. Lawn SD, Harries AD, Anglaret X, Myer L, Wood R. Early mortality among adults accessing antiretroviral treatment programmes in sub-Saharan Africa. *AIDS* 2008;22:1897–908. doi:10.1097/QAD.0b013e32830007cd PMID:18784453
43. Amuron B, Namara G, Birungi J, Nabiryo C, Levin J, Grosskurth H et al. Mortality and loss-to-follow-up during the pre-treatment period in an antiretroviral therapy programme under normal health service conditions in Uganda. *BMC Public Health* 2009;9:290. doi:10.1186/1471-2458-9-290 PMID:19671185
44. Mofenson L. Challenges in pediatric and adolescent HIV care (abstract 65). In: *Fifteenth Conference on Retroviruses and Opportunistic Infections, Boston, 3-6 February 2008.*
45. van Griensven J, De Naeyer L, Uwera J, Asiimwe A, Gazille C, Reid T. Success with antiretroviral treatment for children in Kigali, Rwanda: experience with health center/nurse-based care. *BMC Pediatr* 2008;8:39. doi:10.1186/1471-2431-8-39 PMID:18831747

Table 1. **Demographic and clinical characteristics of children diagnosed with HIV-1 infection, with or without concurrent HIV-2 infection, and those who initiated antiretroviral therapy (ART) during the Aconda HIV treatment programme, Côte d'Ivoire, 2004–2007**

Characteristic	All children	Aged <18 months	Aged 18–59 months	Aged ≥60 months
At HIV diagnosis[a]	**No. = 1 766**	**No. = 307**	**No. = 586**	**No. = 873**
Median age in months (IQR)	54 (22–98)	9 (4–14)	31 (23–44)	99 (76–135)
No. of females (%)	889 (50.3)	155 (50.5)	276 (47.1)	458 (52.5)
No. with HIV-1 infection only (%)	1757 (99.5)	307 (100)	584 (97.7)	866 (99.2)
No. with both HIV-1 and HIV-2 infections (%)	9 (0.5)	0 (0)	2 (0.3)	7 (0.8)
No. with CD4 cell count available (%)	1378 (78.0)	177 (57.7)	474 (80.9)	727 (83.3)
Median % of CD4 cells (IQR)	15.6 (8–22)	15.3 (11.5–21)	16.4 (11.0–22.3)	14.6 (5.6–22)
Median CD4 count in cells/µl (IQR)	487 (212–840)	800 (462–1240.5)	684 (402–1065)	334 (93–606)
Median blood haemoglobin in g/dl (IQR)	9.2 (8.1–10.1)	9.1 (8.1–9.8)	9.0 (7.9–10)	9.4 (8.3–10.3)
No. who satisfied criteria for starting ART (%)	1142 (64.7)	181 (58.9)	369 (63.0)	592 (67.8)
Clinical criteria	374 (21.2)	45 (14.7)	103 (17.6)	226 (25.9)
Immunological criteria	768 (43.5)	136 (44.3)	266 (45.4)	366 (41.9)
At ART initiation[b]	**No. = 977**	**No. = 145**	**No. = 296**	**No. = 536**
Median age in months (IQR)	63 (27–109)	14 (9–16.75)	34 (26–46)	107 (81–139)
No. of females (%)	461 (47.2)	64 (44.1)	130 (43.9)	267 (49.8)
No. with HIV-1 infection only (%)	972 (99.5)	145 (100)	296 (100)	531 (99.1)
No. with both HIV-1 and HIV-2 infections (%)	5 (0.5)	0 (0)	0 (0)	5 (0.9)
Median weight in kg (IQR)	14 (10–21)	7 (6–8.5)	10.6 (9.4–13)	20 (15–25)
Median weight-for-age *z* score (IQR)	–3.0 (–4.7 to –1.8)	–3.7 (–5.4 to –2.5)	–2.70 (–4.5 to –1.4)	–3.11 (–4.7 to –1.8)
Median % of CD4 cells (IQR)	10.7 (5.57–15)	13.0 (9–15.7)	12.0 (8.02–15.75)	8.0 (3–14.5)
Median CD4 cell count in cells/µl (IQR)	359 (106.25–712.75)	714 (475.5–1182.5)	535 (318.5–875)	179 (39–423)
Median blood haemoglobin in g/dl (IQR)	9.2 (8.2–10.3)	9.2 (8.3–10)	9.3 (8.1–10.3)	9.2 (8.2–10.3)
No. with history of tuberculosis treatment (%)	26 (2.7)	3 (2.1)	14 (4.7)	9 (1.7)
No. with ongoing active tuberculosis (%)	32 (3.3)	4 (2.8)	3 (1.0)	25 (4.7)
No. with WHO HIV/AIDS clinical stage 1 or 2 (%)	410 (41.9)	52 (35.9)	136 (45.9)	222 (41.4)
No. with WHO HIV/AIDS clinical stage 3 or 4 (%)	422 (43.2)	57 (39.3)	117 (39.5)	248 (46.3)
No. who received baseline co-trimoxazole prophylaxis (%)	529 (54.2)	95 (65.5)	171 (57.8)	263 (49.1)
No. who received co-trimoxazole prophylaxis after ART (%)	874 (89.5)	128 (88.3)	268 (90.5)	478 (89.2)
No. who received initial ART regimen (%)				
2 NRTIs + 1 NNRTI	636 (65.1)	56 (38.6)	158 (53.4)	422 (78.3)
AZT + 3TC + EFV	240 (24.6)	3 (2.1)	61 (20.6)	176 (32.8)
AZT + 3TC + NVP	39 (4.0)	18 (12.4)	14 (4.7)	7 (1.3)
d4T + 3TC + EFV	279 (28.6)	10 (6.9)	53 (17.9)	216 (40.3)
d4T + 3TC + NVP	70 (7.2)	25 (17.2)	30 (10.1)	15 (2.8)
AZT or d4T or 3TC + DDI + EFV	8 (0.8)	0 (0)	0 (0)	8 (1.5)
2 NRTIs + 1 PI	321 (32.9)	80 (55.2)	133 (44.9)	108 (20.1)
AZT + 3TC + NFV	160 (16.4)	38 (26.2)	63 (21.3)	59 (11.0)
d4T + 3TC + NFV	149 (15.3)	42 (29.0)	65 (22.0)	42 (7.8)
d4T or 3TC or AZT + DDI + NFV	12 (1.2)	0 (0)	5 (1.7)	7 (1.3)
Other	20 (2.0)	9 (6.2)	5 (1.7)	6 (1.1)

3TC, lamivudine; ART, antiretroviral therapy; AZT, azidothymidine; CD4, CD4+ T lymphocyte; d4T, stavudine; DDI, didanosine; EFV, efavirenz; IQR, interquartile range; NFV, nelfinavir; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; NVP, nevirapine; PI: protease inhibitor.

[a] Missing values at HIV diagnosis: sex (no. = 1), CD4 cell percentage (no. = 388), CD4 cell count (no. = 377), blood haemoglobin (no. = 349).

[b] Missing values at ART initiation: sex (no. = 1), weight (no. = 212), weight-for-age *z*-score (no. = 231), CD4 cell percentage (no. = 177), CD4 cell count (no. = 215), blood haemoglobin (no. = 216), WHO HIV/AIDS clinical stage (no. = 145).