Antiretroviral Therapy Outcomes in Resource-Limited Settings for HIV-Infected Children <5 Years of Age

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KEY WORDS
child, developing countries, drug toxicity, highly active antiretroviral therapy, HIV, treatment outcome

ABBREVIATIONS
ART—antiretroviral therapy
CI—confidence interval
IQR—interquartile range
FDC—fixed-dose combination
MSF—Médecins Sans Frontieres (Doctors Without Borders)
WHO—World Health Organization

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WHAT'S KNOWN ON THIS SUBJECT: ART for children with HIV/AIDS in resource-limited settings has been shown to be feasible, but few data exist on ART outcomes in children <5 years of age.

WHAT THIS STUDY ADDS: ART for children <5 years of age is feasible in resource-limited settings, with encouraging clinical outcomes. Survival rates were reduced for children <12 months of age, which emphasizes the need for early HIV diagnosis, treatment, and adherence.

abstract

OBJECTIVE: We describe medium-term outcomes for young children receiving antiretroviral therapy (ART) in resource-limited countries.

METHODS: Analyses were conducted on surveillance data for children <5 years of age receiving ART (initiated April 2002 to January 2008) in 48 HIV/AIDS treatment programs in Africa and Asia. Primary outcome measures were probability of remaining in care, probability of developing World Health Organization stage 4 clinical events, rate of switching to second-line ART, and drug toxicity, compared at 6, 12, 24, and 36 months of ART.

RESULTS: Of 3936 children (90% in Africa) initiating ART, 9% were <12 months, 50% were 12 to 35 months, and 41% were 36 to 59 months of age. The median time of ART was 10.5 months. Probabilities of remaining in care after 12, 24, and 36 months of ART were 0.85, 0.80, and 0.75, respectively. Compared with children 36 to 59 months of age at ART initiation, probabilities of remaining in care were significantly lower for children <12 months of age. Overall, 55% and 69% of deaths and losses to follow-up occurred in the first 3 and 6 months of ART, respectively. Probabilities of developing stage 4 clinical events after 12, 24, and 36 months of ART were 0.03, 0.06, and 0.09, respectively. Only 33 subjects (0.8%) switched to second-line regimens, and 151 (3.8%) experienced severe drug toxicities.

CONCLUSIONS: Large-scale ART for children <5 years of age in resource-limited settings is feasible, with encouraging clinical outcomes, but efforts should be increased to improve early HIV diagnosis and treatment. *Pediatrics* 2010;125:e1039–e1047

By the end of 2007, the Joint United Nations Program on HIV/AIDS reported that 2.1 million children <15 years of age were living with HIV/AIDS throughout the world, with 90% in sub-Saharan Africa.[1] Despite recent increases in antiretroviral therapy (ART) in resource-limited settings, coverage for children has been significantly less than that for adults; of the 3 million people receiving ART by the end of 2007, only 6.6% (198 000 people) were children.[1]

In most rural contexts in resource-limited settings, services to prevent HIV transmission from pregnant women to their infants are not present, are not accessed, or function poorly.[2,3] Consequently, many HIV-positive children become infected perinatally or during breastfeeding. Approximately 50% of vertically infected children would die before the age of 2 without treatment, with mortality rates increasing to 75% by 5 years of age.[4,5] In the absence of well-integrated maternal and child health and HIV activities, many HIV-infected children are neither diagnosed nor treated in time. The lack of age- and context-appropriate diagnostic tools, small numbers of trained providers, and limited access to pediatric drug formulations contribute to delays in treatment in these settings.

An increasing number of studies report ART success for HIV-infected children living in resource-limited settings.[6,7] However, most studies involve relatively small numbers of children, have median ages at ART initiation of >5 years, and provide little information on clinical outcomes.[6] Few studies have focused on outcomes in the critical first years of life.

Doctors Without Borders/Médecins Sans Frontieres (MSF) began providing ART in resource-limited settings in 2000. By the middle of 2008, MSF was treating >140 000 patients with ART in 27 countries, with ~10 000 patients being <15 years of age and >4000 being <5 years of age. This study details ART outcomes for HIV-infected children <5 years of age, stratified according to age groups, in MSF programs in Africa and Asia.

METHODS

Setting and Participants

Children <5 years of age who began to receive ART in African or Asian MSF programs between April 2002 and January 2008 were eligible for the analysis. Programs with <5 children receiving ART were excluded. Age groups were defined according to age at ART initiation, that is, 0 to 11, 12 to 34, or 35 to 59 months.

Information from 48 MSF programs in 20 countries was included. African programs included those in Benin, Burkina Faso, Cameroon, Republic of the Congo, Côte d'Ivoire, Democratic Republic of the Congo, Guinea, Kenya, Liberia, Malawi, Mozambique, Nigeria, Uganda, Zambia, and Zimbabwe. Asian programs were those in Myanmar (Burma), Cambodia, China, India, and Laos.

All programs provided HIV counseling and testing and free medical care including ART, laboratory investigations, and management of opportunistic infections. For children >18 months of age, HIV infection was diagnosed on the basis of 2 positive rapid antibody tests; for children <18 months of age, HIV diagnosis was based on immunologic and clinical criteria as recommended by the World Health Organization (WHO) or was established through RNA or proviral DNA polymerase chain reaction tests using dried blood spots, when this technique was available.[2] Daily cotrimoxazole prophylaxis was prescribed routinely, according to WHO criteria.[2,8] All programs collected patient monitoring data, in agreement with the Ministry of Health, and oral consent was obtained at treatment initiation.

ART Eligibility and Regimens

Criteria for starting ART and first-line ART regimens were based on WHO recommendations.[5,6] ART formulations were mainly adult, generic stavudine-based, fixed-dose combination (FDC) tablets, whole or cut in half if children weighed 10 to 25 kg,[9] with syrups for those weighing <10 to 14 kg. Pediatric FDC drugs were used as soon as they were prequalified by the WHO (July 2007).

Children were clinically examined at least monthly during the first 6 months of ART and then every 2 to 3 months after stabilization on treatment. Adherence support included designation of 1 caregiver, intensive pre-ART education, and regular treatment adherence sessions for both child and caregiver. Where available, $CD4^+$ cell count measurements were performed every 6 to 12 months, using FacsCount (BD, Franklin Lakes, NJ), Partec (Partec, Munster, Germany), or Dynabeads (Invitrogen, Carlsbad, CA). Because of limited availability in the field and cost, HIV viral loads were not systematically determined.

WHO clinical staging used in the study was based on 2006 guidelines.[5] Clinical events reported were based on clinical diagnoses with or without biological confirmation, depending on the facilities available. Severe immunosuppression was defined according to 2006 WHO age-related thresholds, that is, proportions of $CD4^+$ cells of <25% for children <12 months of age, <20% for children 12 to 35 months of age, and <15% for children 36 to 59 months of age.[2]

"ART-naive" was defined as having no previous ART exposure, including exposure through interventions for prevention of mother-to-child transmission. Patients were considered to be receiving a second-line ART regimen if, after >6 months of treatment with a nonnucleoside reverse transcriptase

inhibitor-based, first-line regimen, they were switched to a protease inhibitor-containing regimen with a concomitant change of ≥1 nucleoside reverse transcriptase inhibitor. Severe antiretroviral drug toxicity was defined as an adverse event related to the particular antiretroviral drug that resulted in substitution with an alternative antiretroviral agent.

Data Collection

Data were collected and entered into Fuchia monitoring software (Epicenter, Paris, France), which is used in most Doctors Without Borders HIV/AIDS programs. Variables collected included gender, age, previous and current antiretroviral agents, visit dates, WHO clinical stage, previous and current clinical events, drug intolerance, $CD4^+$ cell counts and $CD4^+$ cell proportions, weight, and height.

Statistical Analyses

Probabilities of remaining in care were calculated by using death and loss to follow-up monitoring as combined end points through the Kaplan-Meier method. Patients were considered lost to follow-up monitoring if they missed their scheduled visit by >2 months. Incidence rates were expressed in child-years of follow-up monitoring during ART for a given time and population group. For incidence calculations, the first event (WHO stage 4 clinical event, switch to second-line treatment regimen, or drug toxicity) occurring during a given period was considered. Comparisons of proportions were performed by using the χ^2 test and medians by using Kruskal-Wallis tests. Analyses were performed with Stata 8.1 (Stata Corp, College Station, TX).

RESULTS

Patient Characteristics at ART Initiation

Between April 2002 and January 2008, 3936 HIV-infected children <5 years of age began ART in MSF programs; 3537 (89.8%) were in Africa and 399 (10.1%) in Asia. A total of 335 children (8.5%) <12 months of age, 1971 (50.1%) 12 to 35 months of age, and 1630 (41.4%) 36 to 59 months of age initiated ART. Nearly all were naive to ART, the majority were classified as being in WHO clinical stage 3, most had severe immunosuppression, and many in Asia had active tuberculosis (Table 1).

The main ART regimen for children 12 to 59 months of age was stavudine/lamivudine/nevirapine. For the age group of <12 months, zidovudine/lamivudine/nevirapine was the most prescribed regimen (Table 1).

Overall, baseline $CD4^+$ cell count data were available for 65% of children. The cohort of children without $CD4^+$ cell count information was similar, in terms of probability of remaining in care, to the cohort with $CD4^+$ cell count data at baseline (log rank test, $P = .27$). Larger proportions of children <12 months of age, compared with children 36 to 59 months of age, had severe immunosuppression at ART initiation in African (91.7% vs 74.1%; $P < .001$) and Asian (88.9% vs 72.6%; $P = .05$) programs (Table 1). Total ART follow-up times were 3979 children-years in Africa and 583 children-years in Asia, with a median follow-up time of 10.5 months (interquartile range [IQR]: 3.7–20.6 months).

Probabilities of Remaining in Care

At the time of analysis, 2971 (75.5%) children were still being monitored in the program, 249 (6.3%) had died, 407 (10.3%) were lost to follow-up, 305 (7.8%) had transferred out, and 4 (0.10%) had unclear outcomes. Overall probabilities of survival were 0.93 (95% confidence interval [CI]: 0.92–0.94; $n = 1758$), 0.92 (95% CI: 0.90–0.93; $n = 862$), and 0.90 (95% CI: 0.88–0.91; $n = 304$) after 12, 24, and 36 months of ART, respectively; probabilities of remaining in care were 0.85 (95% CI: 0.84–0.86), 0.80 (95% CI: 0.78–0.81), and 0.75 (95% CI: 0.73–0.77), respectively. Compared with children 36 to 59 months of age at ART initiation, probabilities of survival (log rank test, $P < .001$) and remaining in care (log rank test, $P < .001$) were significantly lower for children <12 months of age. In addition, the probability of remaining in care after 12 months of ART was significantly higher in Asian programs (0.93 [95% CI: 0.89–0.95]; $n = 215$) than in African programs (0.84 [95% CI: 0.83–0.85]; $n = 1543$; log rank test, $P < .001$) (Fig 1).

Overall, 55% ($n = 353$) of deaths and losses to follow-up monitoring occurred during the initial 3 months of ART and 69% ($n = 442$) occurred during the initial 6 months. Findings were not significantly different when stratified according to age group or continent.

Probabilities of Clinical Events During ART

The probability of developing WHO stage 4 clinical events in the first 6 months of ART was 0.05 (95% CI: 0.04–0.05; $n = 2368$; 141 events), with severe bacterial infections (36%), cachexia (21%), and extrapulmonary tuberculosis (18%) being the most frequently reported diagnoses. The incidences of WHO stage 4 clinical events were highest in the first 6 months of ART in both Africa and Asia and in all age groups (Table 2).

When only events that occurred after 6 months of ART were considered, probabilities of developing WHO stage 4 clinical events were 0.03 (95% CI: 0.02–0.03; $n = 1714$), 0.06 (95% CI: 0.05–0.07; $n = 804$), and 0.09 (95% CI: 0.07–0.11; $n = 278$) after 12, 24, and 36 months of ART, respectively. Again, the most frequently reported clinical events were severe bacterial infec-

TABLE 1 Baseline Characteristics of Children <59 Months of Age Receiving ART in Doctors Without Borders African and Asian HIV/AIDS Programs

	Africa ($N = 3537$)			Asia ($N = 399$)			Total ($N = 3936$)
	<12 mo ($N = 307$)[a]	12–35 mo ($N = 1818$)[a]	36–59 mo ($N = 1412$)[a]	<12 mo ($N = 28$)[a]	12–35 mo ($N = 153$)[a]	36–59 mo ($N = 218$)[a]	
Female, *n* (%)	145 (47.4)	861 (47.5)	663 (47.0)	10 (35.7)	71 (46.4)	105 (48.4)	1855 (47.1)
ART-naive, *n* (%)	290 (94.5)	1769 (97.3)	1364 (96.6)	28 (100)	148 (96.7)	205 (94.0)	3804 (96.7)
Antecedent tuberculosis, *n* (%)	29 (9.5)	293 (16.1)	258 (18.3)	3 (10.7)	51 (33.3)	67 (30.7)	701 (17.8)
Current tuberculosis, *n* (%)	10 (3.3)	104 (5.7)	106 (7.5)	11 (39.3)	38 (24.8)	33 (15.1)	302 (7.7)
Delay between cohort inclusion and ART initiation, median (IQR), mo	0.9 (0.2–2.6)	1.4 (0.4–4.9)	2.3 (0.7–6.9)	2.9 (1.0–5.6)	1.9 (0.2–5.6)	2.4 (0.2–5.8)	1.7 (0.5–5.2)
WHO pediatric staging, *n* (%)[b]							
Unknown	39 (12.7)	203 (11.2)	147 (10.4)	3 (10.7)	18 (11.8)	22 (10.1)	432 (11.0)
Stage 1	28 (9.1)	156 (8.6)	129 (9.1)	0 (0)	8 (5.2)	19 (8.7)	340 (8.6)
Stage 2	23 (7.5)	207 (11.4)	203 (14.4)	0 (0)	14 (9.2)	33 (15.1)	480 (12.2)
Stage 3	149 (48.5)	812 (44.7)	648 (45.9)	19 (67.9)	63 (41.2)	88 (40.4)	1779 (45.2)
Stage 4	68 (22.2)	440 (24.2)	285 (20.2)	6 (21.4)	50 (32.7)	56 (25.7)	905 (23.0)
Age at baseline, median (IQR), y	0.7 (0.5–0.9)	2.0 (1.6–2.4)	4.0 (3.4–4.3)	0.6 (0.6–0.9)	2.1 (1.8–2.5)	4.0 (3.4–4.3)	2.6 (1.7–3.7)
Weight at baseline, median (IQR), kg	6.0 (5.0–7.7)	9.2 (7.5–11.0)	13.0 (11–15)	7.0 (5.9–7.5)	9.0 (8.0–10.0)	12.0 (10–13)	10.1 (8.0–13.0)
Initial ART regimen, *n* (%)							
Stavudine/lamivudine/nevirapine	122 (39.7)	985 (54.2)	1041 (73.7)	9 (32.1)	84 (54.9)	151 (69.3)	2392 (60.8)
Stavudine/lamivudine/efavirenz	4 (1.3)	30 (1.7)	108 (7.7)	6 (21.4)	24 (15.7)	41 (18.8)	149 (3.8)
Zidovudine/lamivudine/nevirapine	153 (49.8)	670 (36.9)	224 (15.9)	7 (25.0)	35 (22.9)	21 (9.6)	1110 (28.2)
Zidovudine/lamivudine/efavirenz	2 (0.7)	33 (1.8)	20 (1.4)	2 (7.1)	3 (2.0)	3 (1.4)	63 (1.6)
Other	26 (8.5)	100 (5.5)	19 (1.4)	4 (14.3)	7 (4.6)	2 (0.9)	158 (4.0)
Severe anemia (hemoglobin level of <7.5 g/dL), *n*/*N* (%)	20/115 (17.4)	91/722 (12.6)	53/609 (8.7)	2/15 (13.3)	6/66 (9.1)	2/82 (2.4)	174/1609 (10.8)
Immunologic status, *n*/*N* (%)							
Severe immunosuppression[b]	154/168 (91.7)	953/1094 (87.1)	613/823 (74.5)	16/18 (88.9)	81/96 (84.4)	106/146 (72.6)	1923/2345 (82.0)
Strong immunosuppression (<5% $CD4^+$ cells)	17/168 (10.1)	95/1094 (8.7)	100/823 (12.1)	3/18 (16.7)	10/96 (10.4)	36/146 (24.7)	261/2345 (11.1)
Nutritional status							
Severely malnourished (weight-for-age *z* score below −3), *n*/*N* (%)	78/193 (40.4)	439/1105 (39.7)	127/760 (16.7)	5/15 (33.3)	20/85 (23.5)	40/121 (33.1)	709/2279 (31.1)
Weight-for-age *z* score indicator, median (IQR)	−2.6 (−3.6 to −1.3)	−2.6 (−3.7 to −1.5)	−1.7 (−2.6 to −0.8)	−1.9 (−3.4 to −0.4)	−2.5 (−3.0 to −1.5)	−2.6 (−3.3 to −1.7)	−2.3 (−3.3 to −1.2)

[a] Age at ART initiation.

[b] Calculations were made according to thresholds recommended in WHO 2006 guidelines (<25% for <12 months of age, <20% for 12–35 months of age; and <15% for 36–59 months of age).

tions (65.3%), cachexia (14.5%), and extrapulmonary tuberculosis (8.9%). Events occurred after a median time of 13.8 months (IQR: 8.7–21.7 months).

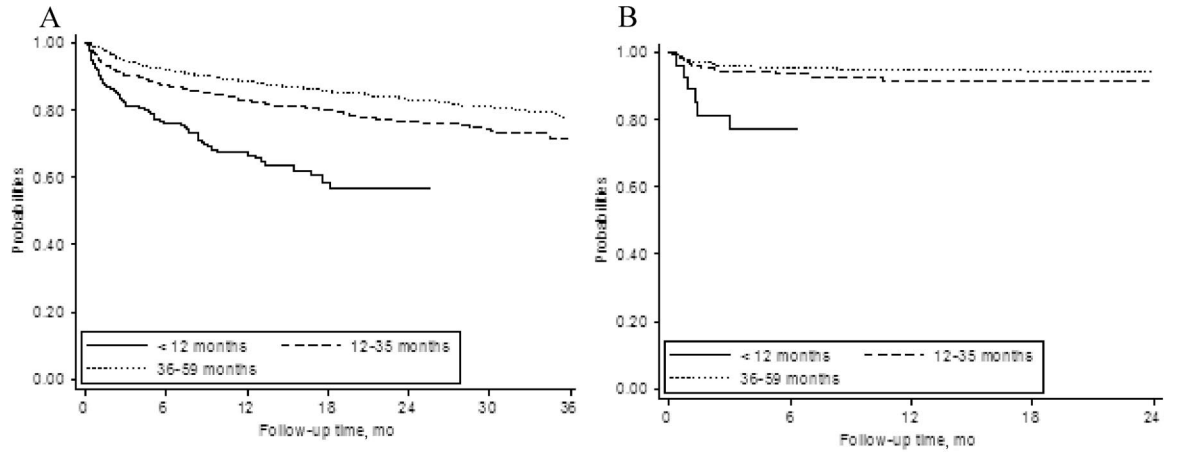
Second-Line ART Regimens

A total of 33 patients (0.8%) were switched to a second-line ART regimen, after a median time of 27.3 months (IQR: 17.4–30.4 months). Most of these switched patients were in Africa ($n = 29$ [87.9%]). Thirteen (39.4%) were 12 to 35 months of age at ART initiation, and 20 (60.0%) were 36 to 59 months of age. The overall incidence of switching was 0.7 cases per 100 person-years (95% CI: 0.5–1.0 cases per 100 person-years), and rates did not differ significantly between continents or age groups. The probability of remaining on first-line regimen after 24 months of ART was 0.99 (95% CI: 0.98–0.99); values were not significantly different when stratified according to continent or age at ART initiation.

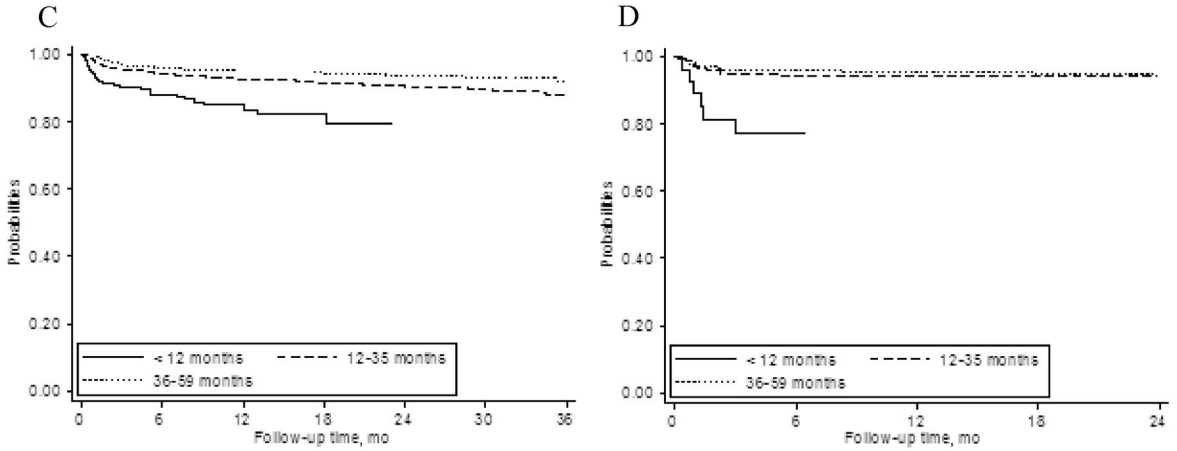
Drug Toxicity

A total of 151 children (3.8%) changed ≥1 of their first-line antiretroviral agents because of severe toxicity. The probabilities of remaining free of severe toxicity were 0.97 (95% CI: 0.96–0.97; $n = 2391$), 0.96 (95% CI: 0.95–0.97; $n = 1691$), 0.95 (95% CI: 0.94–0.96; $n = 810$), and 0.94 (95% CI: 0.93–0.95) at 6, 12, 24, and 36 months of ART, respectively. The median time of ART at the time of antiretroviral drug change was 1.4 months (IQR: 0.7–5.7 months).

In the first 6 months of ART, toxicities were more frequent in Asia than in Africa (0.93 vs 0.97; log rank test, $P < .001$). Severe toxicities were significantly more frequent with zidovudine than with stavudine in African children 12 to 59 months of age ($P < .001$), with a median weight of 8.1 kg (IQR: 7.2–9.5 kg). In Asia, toxicities tended



Months of ART	M12	M24	M36	M12	M24	M36
Age groups						
<12 months						
n at risk	74	20		10		
Probability	0.68	0.57		0.73		
95% CI	0.60-0.74	0.47-0.65		0.51- 0.86		
12-35 months						
n at risk	689	329	116	75	38	16
Probability	0.83	0.76	0.72	0.92	0.92	0.92
95% CI	0.81-0.85	0.73-0.79	0.68-0.75	0.85-0.95	0.85- 0.95	0.85- 0.95
36-59 months						
n at risk	782	396	136	132	77	35
Probability	0.88	0.83	0.78	0.95	0.94	0.94
95% CI	0.86- 0.90	0.80- 0.85	0.74- 0.81	0.91- 0.97	0.90- 0.97	0.90- 0.97



Months of ART	M12	M24	M36	M12	M24	M36
Age groups						
<12 months						
n at risk	74	20		10		
Probability	0.85	0.80		0.73		
95% CI	0.79-0.89	0.71-0.86		0.51-0.86		
12-35 months						
n at risk	689	329	116	75	38	16
Probability	0.93	0.90	0.88	0.94	0.94	0.94
95% CI	0.91-0.94	0.88-0.92	0.84-0.90	0.89-0.97	0.88-0.97	0.89-0.97
36-59 months						
n at risk	782	396	136	132	77	35
Probability	0.95	0.94	0.92	0.96	0.95	0.95
95% CI	0.94-0.96	0.92-0.95	0.90-0.94	0.92-0.98	0.90-0.97	0.90-0.97

FIGURE 1

A and B, Probabilities of remaining in care for children in African (A) and Asian (B) MSF HIV/AIDS programs, according to age at ART initiation. C and D, Probabilities of survival for children in African (C) and Asian (D) MSF HIV/AIDS programs, according to age at ART initiation.

TABLE 2 Incidence of WHO Stage 4 Clinical Events Among Children According to Age at ART Initiation

	Africa			Asia		
	<12 mo	12–35 mo	36–59 mo	<12 mo	12–35 mo	36–59 mo
Between initiation and 6 mo of ART						
No. of child-years	92	664	556	9	60	86
No. of children with stage 4 events	10	60	49	2	10	12
No. of stage 4 events per child-year, estimate (95% CI)	10.9 (5.3–20.2)	9.0 (7.0–11.6)	8.8 (6.7–11.7)	21.1 (5.3–84.5)	16.6 (8.9–30.8)	14.6 (8.5–25.2)
Between 6 and 12 mo of ART						
No. of child-years	48	426	440	N/A	45	72
No. of children with stage 4 events	3	20	25		2	6
No. of stage 4 events per child-year, estimate (95% CI)	6.3 (2.0–19.5)	4.7 (3.0–7.3)	5.7 (3.8–8.4)		4.5 (1.1–17.8)	8.3 (3.7–18.5)
After 1 y of ART						
No. of child-years	43	712	854	N/A	87	168
No. of children with stage 4 events	2	29	30		2	5
No. of stage 4 events per child-year, estimate (95% CI)	4.7 (1.2–18.8)	4.1 (2.8–5.9)	3.5 (2.5–5.0)		2.3 (0.6–9.2)	3.0 (1.2–7.1)

to be more frequent with nevirapine-containing regimens (Table 3).

After 6 months, only 39 children (30 in Africa and 9 in Asia) experienced a severe drug-related adverse event, at a median time of 16 months (IQR: 10–26 months). Nevirapine was implicated in 17 cases (43.6%) and stavudine in 9 (23.1%).

DISCUSSION

In our study, the probability of remaining in care after 3 years of ART for children 12 to 59 months of age was similar to that reported for adults and older children from MSF and other African cohorts in similar settings.[6,10–16] In Asia, our reported survival rates for children 12 to 59 months of age were higher than those reported after 2 years of treatment for Thai and Cambodian children,[17,18] as well as adults.[19] However, our results suggest that the probability of remaining in care is significantly reduced for children <12 months of age, compared with those who are older at ART initiation. In a study of South African children, older age at therapy initiation was associated with increased virological suppression.[11] This may be explained by mortality rates for HIV-infected children being highest in the first year of life,[2] which suggests that those who are still alive without treatment at >12 months of age have a survival advantage and may have better treatment outcomes. In addition, the relatively older median baseline age of 8 months at ART initiation for the <12-month age group in our analysis might have affected the subjects' survival outcomes adversely, because evidence showed that young infants (3–6 months of age) for whom ART was initiated experienced better outcomes. An Italian study showed that infants for whom ART was initiated at <6 months of age experienced better virological, immunologic, and clinical outcomes than did those with initiation at >6 months of age, despite equivalent HIV viral loads and $CD4^+$ cell counts.[20] Data from the Children With HIV Early Antiretroviral Therapy trial[21] showed that initiation of ART within the first 12 weeks of life, rather than at the

TABLE 3 Incidence of Antiretroviral Agent Toxicities During First 6 Months of Treatment According to Age at ART Initiation

	Africa			Asia		
	<12 mo	12–35 mo	36–59 mo	<12 mo	12–35 mo	36–59 mo
Stavudine toxicity						
No. of events per 100 child-years, estimate (95% CI)	0	0.78 (0.25–2.41)	0.21 (0.03–1.49)	N/A	2.18 (0.31–15.5)	1.2 (0.2–8.4)
No. of child-years	40	386	478		46	84
No. of events	0	3	1		1	1
Zidovudine toxicity						
No. of events per 100 child-years, estimate (95% CI)	3.8 (0.9–15.1)	4.3 (2.4–7.5)	2.8 (0.9–8.6)	N/A	N/A	N/A
No. of child-years	53	282	108			
No. of events	2	12	3			
Nevirapine toxicity						
No. of events per 100 child-years, estimate (95% CI)	0	1.9 (1.1–3.4)	3.8 (2.5–5.9)	N/A	10.1 (4.2–24.3)	8.3 (3.7–18.5)
No. of child-years	84	617	523		50	72
No. of events	0	12	20		5	6
Efavirenz toxicity						
No. of events per 100 child-years, estimate (95% CI)	N/A	7.2 (1.8–28.8)	0	N/A	0	0
No. of child-years		28	55		11	19
No. of events		2	0		0	0

previously WHO-recommended CD4+ cell threshold of 20%,[8] decreased the risk of death by 75%. Finally, the larger proportion of patients with severe immunosuppression in the <12-month age group also likely contributed to the worse outcomes with ART in this age group.

The short interval between first consultation and ART initiation (1–2 months) for infants suggests that failure to initiate ART in the first few months of life was influenced more by a delay in HIV diagnosis than by delays in ART initiation by clinicians. This may be related to several issues, including delayed presentation of HIV-exposed infants to the clinic, lack of awareness of HIV-related illness by caregivers and care providers, and lack of easy-to-use tools for HIV diagnosis in infants.[22] Reinforcing the follow-up care of high-risk infants born to HIV-positive mothers especially needs to be addressed, preferably through HIV-specific services integrated into maternal and child health clinics or primary health care centers or family-friendly services in HIV clinics.[23] Integrating HIV screening into WHO Expanded Programs on Immunization in high-prevalence settings may be an option to increase HIV screening at very early ages.

The reduced probability of remaining in care for the youngest children may reflect poorer treatment adherence in this age group. For the youngest children, treatment success is strongly linked to caregiver involvement and capacity; sickness, education level, and living conditions of caregivers, residence in an orphanage, and interference with daily routines all influence adherence.[24–27] Furthermore, children weighing <10 kg received antiretroviral drugs in syrup formulation and dosages were weight dependent, which often resulted in the use of bulky, heavy bottles of antiretroviral agents that posed logistic challenges in terms of transport and storage by the caregiver. In addition, administering different quantities of different syrups to children is complex and challenging, because of patient refusal (taste), regurgitation, and hygiene issues. In our experience, these issues for caregivers may lead to (1) inaccurate administration of antiretroviral agents, increasing the risks of antiretroviral resistance,[28] overdosing, or toxicity and hence increasing mortality rates, or (2) potential increases in the risk of defaulting from care.

Fortunately, the situation has improved somewhat with the recent availability of quality-ensured FDCs of 3 antiretroviral drugs that can be given to children weighing as little as 3 kg.[29,30] However, development of child-adapted formulations and FDCs for other antiretroviral agents is needed to provide more treatment options and easier, more-appropriate, and more-accurate drug administration. This need is even more relevant in light of recent WHO recommendations calling for protease inhibitor-based ART for infants exposed to nevirapine through interventions for prevention of mother-to-child transmission.[31] For better adherence, more counseling tools adapted to caregivers and young children need to be developed and the involvement of persons living with HIV/AIDS at the community level should be encouraged.

In our study, the probabilities of remaining in care were lower in African programs than in Asian programs, with 73% and 91% of patients, respectively, still receiving ART after 3 years. Favorable outcomes were observed for children in Asian programs, despite a higher level of baseline severe immunosuppression and a higher rate of concurrent active tuberculosis, compared with African programs.[32] However, undiagnosed tuberculosis might have been frequently present before ART initiation in African cohorts, leading to increased rates of early death, compared with Asian cohorts, through immune reconstitution or lack of treatment. In addition, compared with Asian programs, MSF African programs generally are located in areas with higher HIV prevalence and less-developed health care infrastructure and have fewer resources and qualified staff members.

The incidence of new WHO stage 4 clinical events decreased with time of ART. It was highest during the first 6 months, when infections present before ART initiation were likely to play a role.[33] However, the most common clinical diagnoses reported during this period were similar to those reported after 6 months. Little has been published on the incidences and types of clinical conditions among children receiving ART in these settings. A study from Kenya reported that the main causes of death for children receiving ART were pneumonia and diarrhea.[34] In view of our results, minimizing the incidence of bacterial infections, tuberculosis, and cachexia is important for children during the first months of ART. This necessitates improving the diagnosis and treatment of tuberculosis before ART initiation, through better clinical assessment and improved diagnostic tools for young children, which are currently lacking. In addition, routine prescription of and good adherence to cotrimoxazole prophylaxis, as well as nutritional support, are important.

We reported a high probability of young children continuing to receive first-line regimens for the first 2 years of ART, with low rates of switching to second-line regimens. However, CD4+ cell count measurements and clinical evaluation have low sensitivity for detecting virological failure.[35,36] Increasing access to virological monitoring to allow earlier detection of treatment failure may increase rates of switch-

ing in the future. Furthermore, if antiretroviral agents become less costly, better adapted for children, and available in FDCs, this will offer clinicians more options to change regimens earlier if necessary.[37]

As observed in other studies, ART for children seems to be well tolerated, with few severe drug toxicities reported.[18,38,39] Most intolerances occurred during the first 6 months of treatment. In African programs, zidovudine was the antiretroviral drug most commonly associated with severe toxicity. This may be related to the increased risk of underlying anemia attributable to coinfection with malaria and underlying malnutrition. Severe nevirapine- and stavudine-related toxicities were not reported often, particularly for the youngest children, but might have been underestimated because of underreporting.

This study has several limitations. Firstly, our findings are based on data compiled from many African and Asian programs in different environments, and case definitions, clinical practices, counseling methods, and access to laboratory facilities likely varied from one site to another. Secondly, despite encouraging clinical outcomes with ART, we are unable to comment on rates of HIV virological suppression in the absence of viral load monitoring. Finally, we were unable to assess the impact of adherence on studied outcomes.

CONCLUSIONS

Our study adds to the existing evidence that ART for children <5 years of age is feasible, with encouraging clinical outcomes in resource-limited settings. However, survival probabilities were relatively reduced for children <12 months of age, which emphasizes the need for increased efforts to improve early HIV diagnosis and treatment in this young age group.

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