Treatment Outcomes Stratified by Baseline Immunological Status among Young Children Receiving Nonnucleoside Reverse-Transcriptase Inhibitor–Based Antiretroviral Therapy in Resource-Limited Settings

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A study of 568 children aged <5 years who commenced nonnucleoside reverse-transcriptase inhibitor–based antiretroviral therapy in resource-limited settings revealed good early outcomes. After 12 months of antiretroviral therapy, survival probability was 0.89 (95% confidence interval, 0.86–0.92), with no significant difference among children stratified on the basis of baseline immunological levels; 62% attained a CD4 cell percentage >25%, and 7% continued to have a CD4 cell percentage <15%.

Antiretroviral therapy (ART) substantially reduces HIV-related mortality and morbidity in children living in resource-rich settings [1]. Despite large numbers of children in urgent need [2] and high mortality rates among children who do not receive treatment [3], in resource-limited settings, very few children have had access to ART. Although the limited available data suggest good early outcomes among children receiving ART, these studies involve only small numbers of young children [4, 5].

The World Health Organization (WHO) [6] guidelines recommend initiating ART in all children with a CD4 cell percentage <15%, regardless of their clinical status. This is based on observational data from cohorts of children in resource-rich settings where those with a CD4 cell percentage <15% had a higher risk of progression to AIDS or death, compared with those with a CD4 cell percentage ⩾15% [7].

We performed a retrospective analysis of program data from resource-limited settings in 14 countries to report treatment outcomes among young children (age, 18–59 months) with severe or profound immunosuppression on the basis of CD4 cell percentage criteria at the time of commencement of nonnucleoside reverse-transcriptase inhibitor–based ART and to compare these outcomes with those of children with mild-to-moderate immunosuppression.

Patients and methods. We analyzed information from children registered during April 2002–May 2006 in 26 Médecins Sans Frontières HIV/AIDS programs in 14 countries, including 10 in Africa (Benin, Burkina Faso, Democratic Republic of Congo, Kenya, Malawi, Mozambique, Nigeria, Uganda, Zambia, and Zimbabwe) and 4 in Asia (Cambodia, Laos, China, and Myanmar). Eligible children were aged 18–59 months and had a recorded CD4 cell percentage at the time of ART initiation. Children were recruited from programs with ⩾5 children receiving ART and initiated ART >6 months prior to the analysis. HIV/AIDS care was provided for free, with medical doctors, clinical officers, or nurses performing the consultations.

The level of immunosuppression was defined by the CD4 cell percentage level prior to initiation of ART (baseline) and was categorized as profound (<5%), severe (⩾5% to <15%), or mild to moderate (⩾15%). Depending on program conditions, CD4 cell percentage was calculated using either automated or manual methods, with quality control in place. We calculated the change in CD4 cell percentage as the difference between baseline and 12-month measurements for the same child.

All HIV-positive children who met the standard WHO clinical and immunological criteria for starting ART in children were considered eligible to receive ART [8] and initiated ART using standard WHO first-line regimens administered as syrups, single molecules, or as adult, generic fixed-dose combination tablets (Triviro [Ranbaxy]) cut in half [9]. Children were routinely prescribed trimethoprim-sulfamethoxazole prophylaxis according to WHO/UNAIDS guidelines [10]. Antiretroviral naive was defined as no previous antiretroviral exposure, including through prevention of mother-to-child transmission interventions.

Data collection in each of the programs was performed using a standardized data collection form, and data were entered into the Fuchia software (Epicentre-MSF). Datasets were pooled and analyzed using Stata software, version 9.2 (Stata). The char-

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acteristics of patients at initiation of ART according to immunosuppression group were compared using a χ^2 test for categorical variables and a *t* test or Kruskal-Wallis test for continuous variables. Probabilities of survival after initiation of ART were determined using the Kaplan Meier method (with the combined end point of death or loss to follow-up) and compared using the log rank test.

Results. Five hundred eighty-six children were included in the analysis: 93 (16%) had profound, 372 (63%) had severe, and 121 (21%) had mild-to-moderate baseline immunosuppression. Five hundred sixty-nine children (97%) were antiretroviral naive at ART initiation. Characteristics at ART baseline were similar in all categories of immunosuppression, except for median age ($P < .001$) and ART regimen (efavirenz-based; $P < .001$) (table 1).

Three hundred eighty-eight children (66%) commenced a regimen of stavudine, lamivudine, and nevirapine; 135 (23%) received zidovudine, lamivudine, and nevirapine; 40 (7%) received stavudine, lamivudine, and efavirenz; 18 (3%) received zidovudine, lamivudine, and efavirenz; and 5 (<1%) received another regimen. The median duration of administration of ART was 13.9 months (interquartile range [IQR], 7.2–19.7 months), with no significant difference among the groups. At analysis, 470 children (80%) were alive and receiving ART, 34 (6%) were dead, 10 (2%) stopped ART, 47 (8%) were lost to follow-up, 21 (4%) transferred out of the program, and 4 (1%) had unknown outcomes.

The overall probability of survival (death plus loss to follow-up) at 6, 12, and 24 months was 0.92 (95% CI, 0.90–0.94), 0.89 (95% CI, 0.86–0.92), and 0.82 (95% CI, 0.78–0.86), respectively. There were no statistically significant differences among the groups ($P = .15$), even after adjusting for baseline age, sex, Centers for Disease Control and Prevention status, previous ART exposure, acute malnutrition, geographical continent, and ART regimen (table 2). Twenty-six (76%) of 34 deaths occurred within 6 months of commencement of ART (median, 1.4 months; IQR, 0.6–5.6 months). No children were given second-line ART regimens.

After 12 months of receiving ART, 180 (53%) of 338 eligible children had a recorded CD4 cell percentage result. Among these children, the median CD4 cell percentage gain was 18% for those with profound immunosuppression, 16% for those with severe immunosuppression, and 12% for those with mild-to-moderate immunosuppression ($P = .007$). Only 21% of children in the profound immunosuppression group and 6% in the severe immunosuppression group had a CD4 cell percentage <15% (ongoing severe immunosuppression), and close to normal levels of immune function (CD4 cell percentage, >25%) were achieved for 32% of children in the profound immunosuppression group, 63% in the severe immunosuppression group, and 82% in the mild-to-moderate immunosuppression group (112 children [62%] overall). Baseline characteristics of those with and without CD4 cell percentage data at 12 months were similar, except that 28% of the former group were from Asia, compared with 10% in the latter group ($P < .001$).

Discussion. Despite the fact that the great majority of children starting ART in this study were severely immunosuppressed (79%), 8 of 10 children were still alive after 2 years of therapy. Such survival rates are similar to those reported among adults [11] and a small cohort of older children in resource-limited settings [5], and the rates are in sharp contrast to the very high short-term mortality rates reported among similar children in resource-limited settings who are not receiving ART

Table 1. Characteristics at antiretroviral therapy initiation among children stratified on the basis of CD4 cell percentage.

	Baseline CD4 cell percentage (n = 586)			
Characteristic	<5%	⩾5% to <15%	⩾15%	*P*
No. (%) of total patients	93 (16)	372 (63)	121 (21)	
Median CD4 cell percentage (IQR)	2.5 (1.2–4.0)	10.3 (8.0–12.4)	18.7 (16.0–24.8)	
African	67 (72)	307 (83)	99 (82)	.07
Asian	26 (28)	65 (18)	22 (18)	
Female sex	38 (41)	172 (46)	55 (46)	.6
Age, median years (IQR)	3.8 (3.0–4.4)	3.1 (2.4–4.1)	3.1 (2.4–4.0)	<.001
Weight, median kg (IQR)	11 (9.3–13.0)	12 (10–14)	12 (9.5–14)	.63
Proportion of patients with less than −2 weight-height Z score (%)	12/45 (27)	24/194 (12)	12/73 (16)	.06
Proportion of patients with CDC stage C (%)	39/83 (47)	143/338 (42)	44/115 (38)	.47
ARV naive	90 (97)	365 (98)	114 (94)	.08
Received EFV-based regimen at initiation	23 (25)	31 (8)	6 (5)	<.001
Received AZT-based regimen at initiation	27 (29)	86 (23)	41 (34)	.06

NOTE. Data are no. (%) of patients, unless otherwise indicated. ARV, antiretroviral; AZT, zidovudine; CDC, Centers for Disease Control and Prevention; EFV, efavirenz; IQR, interquartile range.

Table 2. Outcomes of antiretroviral therapy (ART) among children stratified on the basis of CD4 cell percentage at baseline.

Characteristic	CD4 cell percentage			*P*
	<5%	⩾5% to <15%	⩾15%	
Probability of length of survival				
6 months				
Probability (95% CI)	0.85 (0.76–0.91)	0.94 (0.91–0.96)	0.92 (0.86–0.96)	.15
No. of patients	74	326	100	
12 months				
Probability (95% CI)	0.83 (0.74–0.90)	0.91 (0.87–0.93)	0.90 (0.83–0.94)	
No. of patients	57	215	71	
24 months				
Probability (95% CI)	0.80 (0.69–0.87)	0.82 (0.75–0.87)	0.86 (0.76–0.92)	
No. of patients	15	55	14	
Median CD4 cell percentage after 12 months of ART (IQR)	20.4 (15.5–30.0)	27.0 (22.0–32.0)	33.0 (27.0–39.0)	<.001
Median CD4 cell percentage increase (IQR)	17.5 (13.8–27.2)	16.0 (11.0–22.6)	12.3 (5.3–18.1)	.007
No. of patients with CD4 cell percentage <15% after 12 months (%)	6 (21)	7 (6)	2 (5)	.005
No. of patients with CD4 cell percentage >25% after 12 months (%)	9 (32)	71 (63)	32 (82)	<.001
Proportion of patients with less than −2 weight-height Z score after 12 months (%)	0/23 (0)	1/78 (1)	1/31 (3)	.61

NOTE. Data for CD4 cell percentage are for 28 children with a CD4 cell percentage <5%, 113 with a CD4 cell percentage ⩾5% to <15%, and 39 with a CD4 cell percentage ⩾15%. IQR, interquartile range.

[3]. Compared with survival rates among children with mild-to-moderate immunosuppression (CD4 cell percentage, ⩾15%), survival rates in those with severe (CD4 cell percentage, ⩾5% to <15%) and profound (CD4 cell percentage, <5%) immunosuppression were similar, despite significantly higher mortality rates without receipt of ART [7]. However, our data suggest that rates might be lower for the profoundly immunosuppressed group, and this warrants further assessment with a larger sample size.

Likewise, the immunological outcomes that resulted from receiving ART were good, with evidence of significant immunological reconstitution in the majority of the cohort. After 1 year of receiving ART, 62% of children with an available CD4 cell percentage attained near normal immune status (CD4 cell percentage, >25%) [12], and only 7% remained at significant risk of life-threatening opportunistic infections or disease (CD4 cell percentage, <15%) [12]. Those with profound immunosuppression had the greatest absolute median increases in CD4 cell percentage, but they attained lower median absolute CD4 cell percentage levels, and a significantly higher proportion remained severely immunosuppressed. This suggests that, although significant improvements in immune function occur irrespective of baseline CD4 cell percentage levels, the greater the level of baseline immunodeficiency, the more likely the patient will remain at risk of opportunistic infections during the first year of receiving ART.

To our knowledge, there are no similar studies from resource-limited settings analyzing immunological outcomes on the basis of baseline CD4 cell percentage levels in young children. However, our results were similar to those published from resource-rich settings [1, 12]—although the children from resource-rich settings were mainly ART nonnaive, had mean ages >6 years, were less immunosuppressed (i.e., the CD4 cell percentage was <15% for 33%–54% of the cohorts), and were treated with mainly protease inhibitor–containing regimens.

Although overall outcomes were good, our findings suggest that better outcomes are achieved if ART is started before profound immunosuppression develops. Measures needed to achieve this include increased access to and offer of HIV testing to ensure early diagnosis of HIV, increased access to CD4 T cell testing methods to identify severely immunosuppressed children before they develop opportunistic infections, greater education of parents and health care workers regarding the benefits of ART for children to encourage earlier presentation to health services, and increased availability of adapted and affordable pediatric medications to make initiation of treatment possible and less complex.

There are a number of study limitations. First, because of the operational constraints of resource-limited settings, most programs had no access to viral load measurements. Therefore, despite the good early survival and immunological outcomes, we cannot exclude the possibility of suboptimal virological suppression resulting in less satisfactory longer-term outcomes. Secondly, we had incomplete data on immunological outcomes

(53% of children had an available CD4 cell percentage at 12 months). This was likely a result of operational constraints in providing CD4 measurements. However, apart from regional differences, the ART baseline characteristics did not differ significantly between those with and without CD4 cell percentage data at 12 months. Thus, we feel that the population with available CD4 immunological outcomes was representative of the overall cohort population. Nevertheless, it is possible that the reported immunological gains were overestimated, because they only consider surviving children and those not lost to follow-up. Thirdly, we do not have ART adherence data to exclude differences in adherence rates among the groups, potentially influencing outcomes. Finally, our cohort represents only children with a known baseline CD4 cell percentage, and because this may have introduced a selection bias, our findings may not be generalizable to a cohort of children in resource-limited settings where baseline CD4 cell percentage is not known.

This study demonstrates that in resource-limited settings, under routine program conditions, administration of nonnucleoside reverse-transcriptase inhibitor–containing ART to severely and profoundly immunosuppressed children can achieve good early outcomes, and these outcomes are comparable to results among mild-to-moderately immunosuppressed children. This provides further impetus to urgently ensure that children in resource-limited settings have early access to life-prolonging ART.

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