In resource-limited settings good early outcomes can be achieved in children using adult fixed-dose combination antiretroviral therapy

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Objectives: To (a) determine early treatment outcomes and (b) assess safety in children treated with adult fixed-dose combination (FDC) antiretroviral tablets.

Setting: Sixteen Medecins Sans Frontieres (MSF) HIV programs in eight countries in resource-limited settings (RLS).

Methods: Analysis of routine program data gathered June 2001 to March 2005.

Results: A total of 1184 children [median age, 7 years; inter-quartile range (IQR), 4.6–9.3] were treated with antiretroviral therapy (ART) of whom 616(52%) were male. At ART initiation, Centres for Disease Control stages N, A, B and C were 9, 14, 38 and 39%, respectively. Children were followed up for a median period of 6 months (IQR, 2–12 months). At 12 months the median CD4 percentage gain in children aged 18–59 months was 15% (IQR, 6–18%), and the percentage with CD4 gain < 15% was reduced from 85% at baseline to 11%. In those aged 60–156 months, median CD4 cell count gain was 275 cells/μl (IQR, 84-518 cells/μl), and the percentage with CD4 < 200 cells/μl reduced from 51% at baseline to 11%. Treatment outcomes included; 1012 (85%) alive and on ART, 36 (3%) deaths, 15 (1%) stopped ART, 89 (8%) lost to follow-up, and 31 (3%) with unknown outcomes. Overall probability of survival at 12 months was 0.87 (0.84–0.89). Side effects caused a change to alternative antiretroviral drugs in 26 (2%) but no deaths.

Conclusions: Very satisfactory early outcomes can be achieved in children in RLS using generic adult FDC antiretroviral tablets. These findings strongly favour their use as an 'interim solution' for scaling-up ART in children; however, more appropriate pediatric antiretroviral drugs remain urgently needed.

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Introduction

There are an estimated 2.3 million children worldwide who are currently living with HIV, the great majority of whom are in resource-limited settings (RLS) [1]. An estimated 660 000 of such children are believed to be in urgent need of life-saving antiretroviral therapy (ART) [2]. Without ART, about 50% of children who are infected with HIV at birth end up dying by their second birthday [3]. Although there are currently more than 1 million adults receiving ART in RLS with very good treatment outcomes, to date, far too few children have been started on treatment in these settings, with estimates of less than 5% of young HIV-positive children who are in need of paediatric AIDS treatment receiving it [3].

Significant obstacles to scaling up ART in children living in RLS include: (a) the lack of human capacity and limited training and experience in treating children, which results in a hesitancy among health staff in starting treatment;

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(b) the lack of practicable, acceptable and available paediatric antiretroviral formulations; (c) no fixed-dose combinations (FDC), nor standardized dosing tables, making treatment more difficult to administer and adhere to [4]; (d) the high cost of paediatric antiretroviral medications, which are up to ten times more expensive than the corresponding adult formulations [5]; and (e) the lack of affordable and simple HIV-diagnostic testing technologies for children under 18 months of age, making diagnosis in young children difficult.

A continuing concern is that few pharmaceutical companies are actually investing in the development of affordable and child-friendly antiretroviral drugs and diagnostics, and this is probably due to the fact that there is a limited burden of HIV/AIDS in children in resource-rich countries.

Medecins Sans Frontieres (MSF) began offering ART in several RLS in 2000, and towards the end of 2005 about 57 000 people were placed on ART in more than 30 countries. Although the main focus of ART was initially on adults, an increasing number of children have been progressively started on ART. As most MSF projects were situated in countries where there was a lack of adapted and affordable paediatric antiretroviral formulations, clinicians were morally obliged to use the available generic adult antiretroviral tablets in order to administer ART to children. In situations where there are no available paediatric alternatives, such a strategy is also supported by the World Health Organisation (WHO) [6].

This study was conducted among children placed on adult FDC antiretroviral tablets under routine program conditions in eight resource-limited countries, in order to (a) determine early outcomes on ART, and (b) assess safety.

Methods

Study setting and population

All eligible HIV-positive children aged < 13 years from 16 MSF-HIV/AIDS clinics in eight countries were included (Cambodia, Kenya, Malawi, Mozambique, Thailand, Uganda, Burkina Faso, and Zimbabwe). The study was carried out between June 2001 (when the first children were placed on ART) and March 2005.

The MSF programs in these countries provide voluntary counselling and HIV testing, and free HIV/AIDS care including the management of opportunistic infections, ART and access to psychosocial support. Children were routinely prescribed cotrimoxazole prophylaxis according to the 2000 UNAIDS guidelines [7]. Programs have a strong ART adherence component, which includes the designation of a specific 'caretaker' to accept overall responsibility for administering antiretroviral drugs to the child, intensive pre-ART education and adherence sessions for the child and caretaker using education tools specifically adapted for children, and peer support group sessions and networks [4,8].

Due to the operational constraints of RLS, at least initially, most programs had limited access to CD4 cell counts and viral load measurement. Therefore children were mostly placed on ART on a clinical basis, and there are limited numbers of children with CD4 cell counts and viral load assessments.

Antiretroviral treatment eligibility and regimens

All HIV-positive children who met the standard WHO clinical and immunological criteria for starting ART in children were considered eligible for treatment [6]. The first-line ART regimen used was the generic FDC tablet Triviro 30 or Triviro 40 (Ranbaxy) containing stavudine (30 or 40 mg), lamivudine (150 mg) and nevirapine (200 mg). Tablets were only administered whole or cut in half; tablets were not broken into quarters and only those children who weighed more than 10 kg were treated. Doses were standardized according to a weight-adjusted dosing schedule as seen in Table 1.

In case of stavudine and nevirapine-related side-effects, the respective alternatives were zidovudine and efavirenz, the later restricted to children over 3 years. Second-line ART was defined as any regimen containing a protease inhibitor and didanosine in line with the National or MSF ART protocols.

Antiretroviral-'naïve' was defined as no previous ART exposure, including exposure through prevention of mother-to-child transmission interventions.

Data collection and statistical analysis

All HIV-positive individuals have a standardized data record and follow up forms, which are part of the patient file. Information collected includes patient demographics, previous medical history, co-existent illness, blood results, treatment and follow-up. This information is entered into the FUCHIA software (epicentre- MSF, Paris) specifically designed for monitoring the care and follow-up of HIV-positive individuals. This data was then pooled, and a multicentric analysis performed using the STATA software 8.2 (STATA Corp., College Station, Texas, USA).

ART outcomes are standardized and include; alive and on ART, death, loss to follow-up, stopped, transferred-out or unknown (Table 2). The immunological status was presented using CD4 percentage (%) measurements for children < 60 months, and absolute CD4 cell counts for those aged 60 months or more. Gain of CD4 cells was defined as the difference between two CD4 measurements for the same children.

Table 1. Weight-based dosing schedule for use of adult fixed-dose combination (FDC) tablets in children.

Child's weight (kg)	FDC regimen	Dose administered with FDC regimen		
		Stavudine	Lamivudine	Nevirapine
10–14	1/2 Triviro 30 BD	30 mg Median 2.5 mg/kg per day Range 2.1–3 mg/kg per day	150 mg Median 12.5 mg/kg per day Range 10.7–15 mg/kg per day	200 mg Median 16.7 mg/kg per day Range 14.3–20 mg/kg per day
15–19	1/2 Triviro 30 BD + 1/2 NVP 200mg OD	30 mg Median 1.8 mg/kg per day Range 1.6–2 mg/kg per day	150 mg Median 8.8 mg/kg per day Range 7.9–10 mg/kg per day	300 mg Median 17.6 mg/kg per day Range 15.8–20 mg/kg per day
20–24	1/2 Triviro 40 BD + 1/2 NVP 200mg OD	40 mg Median 1.8 mg/kg per day Range 1.7–2 mg/kg per day	150 mg Median 6.8 mg/kg per day Range 6.3–7.5 mg/kg per day	300 mg Median 13.6 mg/kg per day Range 12.5–15 mg/kg per day
25–29	1 Triviro 30 BD	60 mg Median 2.2 mg/kg per day Range 2.1–2.4 mg/kg per day	300 mg Median 11.1 mg/kg per day Range 10.3–12 mg/kg per day	400 mg Median 14.8 mg/kg per day Range 13.8–16 mg/kg per day

BD, twice daily; NVP, nevirapine; OD, once daily.

The characteristics of patients at ART initiation between age groups were compared using chi-squared tests for proportions, *t*-tests for mean comparison and K-Wallis test for median comparison. Probabilities of survival and remaining in care at 12 months after ART initiation were calculated using both death only, and death and lost to follow-up, as endpoints. A Kaplan–Meier analysis using the log rank test was performed in order to compare survival between the two age groups.

Results

Characteristics of the study population

A total of 6151 children were registered during the study period of which 2047 were started on ART. A total of 1184 (60%) of the latter were given adult FDC antiretroviral tablets and were thus included in the study. The number of children per project ranged from 11–236; 616 (52%) were male; and the median age was 7 years [inter-quartile range (IQR), 4.6–9.3]. Thirteen (1%) were < 18 months of age, 322 (27%) were aged 18–59 months, and 849 (72%) were aged 59–156 months.

At ART initiation, Centers for Disease Control (CDC) clinical and immunological classification ($n = 1001$) included 9% in stage N, 14% in stage A, 38% in stage B and 39% in stage C. There were no significant differences in the staging between the age-groups 18–59 months and 60–156 months. CD4 cell counts or CD4 percentage were available for 400 (34%) children; 85% of children 18–59 months had a CD4% of < 15, and 51% of children 60–156 months had a CD4 cell count < 200 cells/μl (Table 3). The median weight per height *Z* score ($n = 457$) was −0.6 (IQR, −1.4 to 0.2), with a global acute malnutrition rate (< −2 *Z* score) of 10%. The median height per age *Z* score ($n = 439$) was −2.0 (IQR, −3.2 to −1.1), with a global stunting rate (< −2 *Z* score) of 51%.

Ninety-seven percent of all children were antiretroviral naive at the time of ART commencement. No patients required the commencement of second-line ART.

Antiretroviral treatment outcomes (immunological and clinical)

The median duration on ART was 6.0 months (IQR, 2–12 months), representing 784 person-years of treatment; 606 children (50%) were on ART for a period of less than 6 months, 291 (25%) for 6–12 months, 253 (21%) for 12–24 months and 34 (3%) for over 24 months.

Immunological outcomes at 6 and 12 months stratified into age groups 18–59 months and 60–159 months, respectively, are shown in Table 3. For children aged 18–59 months, the median CD4% gain at 12 months was 15%, and the percentage with CD4% < 15% reduced

Table 2. Standardized monthly treatment outcomes for patients on antiretroviral therapy (ART).

Alive and on antiretroviral treatment	Patient who is alive and has collected his/her own supply of antiretroviral drugs at their last scheduled appointment.
Death	Patient who has died for any reason after commencing ART.
Loss to follow-up (defaulted)	Patient who has commenced ART and has failed to attend the clinic for more than 2 months after the date of their last scheduled appointment.
Stopped	Patient who has stopped ART completely at last visit due to side effects or other reasons
Transfer-out	Patient who has transferred-out permanently to another ART center
Unknown	No date of next appointment recorded and thus status could not be determined.

Table 3. Immunological effects of antiretroviral therapy at 6 and 12 months.

Outcomes	Children aged 18–59 months $N = 322$		Children aged 60–156 months $N = 849$
CD4 at antiretroviral initiation			
CD4%, *N*	95	CD4 absolute, *N*	302
Median (IQR)	9.9 (6.0–13.2)	Median (IQR)	189.5 (73–339)
< 15%	81 (85.3)	< 50	61 (20.2)
15–24%	10 (10.5)	50–199	93 (30.8)
≥ 25%	4 (4.2)	≥ 200	148 (49.0)
CD4 at 6 months			
CD4%, *N*	36	CD4 absolute, *N*	91
Median (IQR)	19.2 (11.8–25.9)	Median (IQR)	516 (307–672)
< 15%	10 (27.8)	< 50	0
15–24%	13 (36.1)	50–199	10 (11.0)
≥ 25%	13 (36.1)	≥ 200	81 (89.1)
Gain CD4% at 6 months		Gain CD4 at 6 months	
N	22	*N*	71
Median (IQR)	11.5 (8.2–14.9)	Median (IQR)	277 (177–388)
CD4 at 12 months			
CD4%, *N*	28	CD4 absolute, *N*	54
Median (IQR)	21.5 (19.4–27.8)	Median (IQR)	517 (334–758)
< 15%	3 (10.7)	< 50	1 (1.9)
15–24%	14 (50.0)	50–199	5 (9.3)
≥ 25%	11 (39.3)	≥ 200	48 (88.9)
Gain CD4% at 12 months		Gain CD4 at 12 months	
N	16	*N*	42
Median (IQR)	14.8 (5.5–17.9)	Median (IQR)	275 (84–518)

from 85% at baseline to 28% at 6 months and 11% at 12 months. For those aged 60–156 months the median CD4 cell gain was 275 cells/μl at 12 months, and the percentage with CD4 cell count < 200 cells/μl reduced from 51% at baseline to 11% at 6 and 12 months. There was no significant difference between the ART baseline CD4 cell levels for those with and without information on CD4 cell count at 6 and 12 months, and the ART baseline level of immunodeficiency did not differ by year of ART initiation.

Treatment outcomes at the end of March 2005 included: 1012 (85%) alive and on ART, 36 (3%) deaths, 15 (1%) stopped ART, 89 (8%) lost to follow-up, one (0.1%) transferred out, and 31 (3%) unknown outcomes.

The overall probability of survival at 12 months with deaths as the endpoint was 0.95 [95% confidence interval (CI), 0.93–0.97]. If deaths and lost to follow-up were combined as the endpoint (since those lost to follow up are likely to end up as deaths), survival probability at 12 months was 0.87 (95% CI, 0.84–0.89).

The overall probability of survival with deaths only as the endpoint was significantly better in the age group 18–59 months than in those aged 60–156 months (log rank test, $P = 0.03$); however, this difference between age groups does not appear using the combined endpoint of death and lost to follow-up (log rank test 0.32) (Fig. 1).

The median duration on ART for children who died was 4.5 months (IQR, 1.9–7.1 months) for those aged 18–59 months, and 2.3 months (IQR, 1.2–5.0 months) for those aged 60–156 months (Table 4).

Adverse side effects (safety)

A total of 46 (4%) of children were reported to have experienced side effects to at least one antiretroviral medication. Most of these were minor and only 26 (2%) merited a change to an alternative first-line ART regimen. The median time on ART before a change to an alternative regimen was 1.4 months (IQR, 0.5–3.2 months). There were no reported deaths attributable to antiretroviral medication.

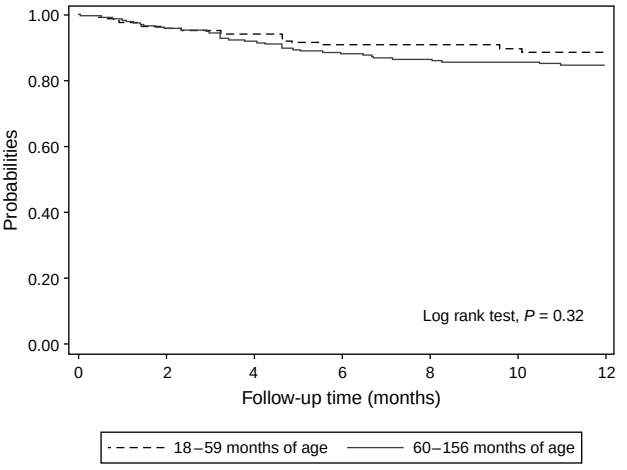

Fig. 1. Probability of survival (endpoint death and loss to follow-up) for children starting antiretroviral therapy with adult fixed-dose combination antiretroviral tablets according to age group.

Table 4. Duration on antiretroviral therapy (ART) for children who have died or been lost to follow-up according to age groups.

Duration on ART	18–59 months old	5–13 years old
Children died	$N = 2$	$N = 34$
Median (IQR), months	4.5 (1.9–7.1)	2.3 (1.2–5.0)
Min–max	1.9–7.9	0.03–11.0
Children lost to follow-up	$N = 27$	$N = 61$
Median (IQR), months	2.3 (0.8–4.6)	3.2 (1.4–4.6)
Min–max	0.03–18.5	0.1–36.0

Discussion

This study shows that generic adult FDC antiretroviral tablets can be successfully used to treat children in urgent need of ART in RLS, and satisfactory short-term outcomes can be achieved under routine program conditions. The clinical and immunological outcomes, and particularly overall survival rates, are similar to that seen in adults on ART in both resource-rich and RLS [9–14].

Of note, our results suggest that young children (18–59 months) do equally as well on treatment as older children (60–156 months) in terms of survival. Although when deaths only was used as the endpoint, the survival in the age group less than 59 months was significantly higher than in the older age group, this is probably not relevant as it is probable that the majority of children that were lost to follow-up had died, and when this was taken into account there was no significant difference in survival between the two age-groups.

There are a number of important operational benefits of using adult FDC antiretroviral drugs. Firstly, they are now available in most ART programs in RLS and thus 'accessible' within the framework of national programs. Secondly, they exist in generic form, are much less costly and thus affordable for scaling-up on a country-wide level. Thirdly, the use of adult FDCs significantly reduces the pill burden as pediatric FDCs are not yet available. This likely facilitates continued adherence and consequently a reduced risk of antiretroviral resistance development. Fourthly, compared to syrups, tablets have a more acceptable taste, and can be swallowed as such, or crushed and mixed with food, facilitating their administration. Finally there is the added consideration that most children and caretakers actually prefer antiretroviral tablets to syrups as the latter are generally of low concentrations requiring children to swallow large volumes of liquids which many end up eventually being vomited or rejected [8].

Despite these advantages, there are still a number of areas of concern regarding the use of adult FDC antiretroviral drugs in children. Firstly, bioequivalence and bioavailability studies using FDCs have only been conducted in adults and the results might not necessarily be applicable to children. Secondly, it is possible that individual molecules of antiretroviral in the FDC may not be uniformly distributed within the tablet. This might have an effect on the amount of individual antiretroviral drug contained within an administered 'fraction' of a tablet. Uneven splitting of the tablet and the possibility of reduced absorption from split tablets, may also lead to eventual inaccuracies in dosing. A further concern is the fact that age-adjusted doses do not evolve in the same way for the three drugs present in the FDC. This might imply that there are real risks of 'under' or 'over-dosing' in some age-group ranges. This is especially important for nevirapine where there is a low genetic barrier to resistance and low plasma concentrations run a significant risk of developing antiretroviral resistance [15]. Reassuringly a recent study examining the use of the adult FDC GPO-VIR in Thailand children showed satisfactory plasma concentrations of NVP [16]. In addition, the tablet is scored and not coated, making it more easy and accurate to split.

A relevant observation is that very few children under 18 months of age started ART with adult FDC tablets, which is linked partly to the fact that children needed to be > 10 kg to qualify, but also to the current lack of easy-to-use HIV diagnostic technologies in this age-group.

There are a number of limitations to this study. Firstly we were not able to measure antiretroviral drug levels to confirm their therapeutic adequacy, and we did not have access to virological monitoring to report on virological outcomes. However, this situation is typical of the operational reality in most RLS where cost, complexity and access issues pose real barriers to such investigations. Nevertheless, as there was a relatively short follow-up period we cannot exclude the possibility of inadequate drug levels resulting in sub-optimal virological suppression and the subsequent development of antiviral resistance mutations. This may result initially in good outcomes, but could lead to less satisfactory longer-term outcomes. Thus further research measuring drug levels and virological outcomes is urgently required.

Another limitation is the limited data on immunological outcomes. However the ART baseline CD4 cell levels did not differ significantly between those with and those without CD4 results at 6 and 12 months, and thus we feel that the population with available CD4 immunological outcomes was representative of the overall population of children. In addition there was no evidence of a cohort effect as the baseline level of immunodeficiency did not change over the years of the study. Nevertheless it remains possible that the reported immunological gains were overestimated since they only take into account surviving children.

Further limitations include a possible under-reporting of antiretroviral adverse effects due to a lack of standardized reporting of these across the projects, and that the results are based on a multicentric analysis comparing programs in different contexts which may have varying operating conditions.

Although MSF has gone ahead and used adult FDCs to administer life-saving ART to children in RLS, and the preliminary results are very encouraging, we feel this situation is 'far from ideal' and does not in anyway replace the urgent need for adapted and affordable pediatric formulations, including those in FDC form, to become available. Advocacy for their urgent development is required.

In the meantime, our findings strongly favour the use of adult FDC antiretroviral drugs as an 'interim solution' for scaling-up ART in children, while waiting for more appropriate pediatric antiretroviral formulations.

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References

1. United Nations Programme on HIV/AIDS (UNAIDS) and World Health Organisation (WHO). *Aids epidemic update: December 2005*. Geneva: UNAIDS and WHO; 2005. pp. 1–90.
2. World Health Organisation. *Progress on global access to HIV antiretroviral therapy. A report on '3 by 5' and beyond*. Geneva: World Health Organisation; March 2006. pp. 1–80.
3. The United Nations Children's Fund (UNICEF). *The global campaign on children and AIDS: Unite for children. Unite against AIDS*. New York: UNICEF; 2005.
4. Ponnet M, Frederix K, Petdachai W, Wilson D, Eksaengsri A, Zachariah R. **A drug dosage table is a useful tool to facilitate prescriptions of antiretroviral drugs for children in Thailand.** *Int J STD AIDS* 2005; **16**:420–426.
5. Medecins Sana Frontieres. *Untangling the web. A guide for prices for purchase of ARV for developing countries*. Geneva: Medecins Sans Frontieres; 2006.
6. World Health Organisation. *Scaling up antiretroviral therapy in resource-limited settings: treatment guidelines for a public health approach (revision)*. Geneva: World Health Organisation, 2004. QV268.5.
7. World Health Organisation; UNAIDS. **Provisional WHO/UNAIDS recommendations on the use of cotrimoxazole prophylaxis in adults and children living with HIV/AIDS in Africa**. *Afr Health Sci* 2001; **1**:30–31.
8. Ponnet M, Nisachol O, Sudrak L, Fredericx K, Wilson D, Zachariah R. **Offering highly active antiretroviral treatment to children: the difficulties.** *Tropical Doctor* 2005; **35**:251.
9. Laurent C, Diakhate N, Gueye NF, Toure MA, Sow PS, Faye MA, *et al*. **The Senegalese government's highly active antiretroviral therapy initiative: an 18-month follow-up study.** *AIDS* 2002; **16**:1363–1370.
10. Tassie JM, Szumilin E, Calmy A, Goemaere E. **Highly active antiretroviral therapy in resource-poor settings: the experience of Medecins Sans Frontieres.** *AIDS* 2003; **17**:1995–1997.
11. Djomand G, Roels T, Ellerbrock T, Hanson D, Diomande F, Monga B, *et al*. **Virologic and immunologic outcomes and programmatic challenges of an antiretroviral treatment pilot project in Abidjan, Cote d'Ivoire.** *AIDS* 2003; **17 (suppl 3)**:S5–S15.
12. Coetzee D, Hildebrand K, Boulle A, Maartens G, Louis F, Labatala V, *et al*. **Outcomes after two years of providing antiretroviral treatment in Khayelitsha, South Africa.** *AIDS* 2004; **18**:887–895.
13. Akileswaran C, Lurie MN, Flanigan TP, Mayer KH. **Lessons learned from use of highly active antiretroviral therapy in Africa.** *Clin Infect Dis* 2005; **41**:376–385.
14. Ivers LC, Kendrick D, Doucette K. **Efficacy of antiretroviral therapy programs in resource-poor settings: a meta-analysis of the published literature.** *Clin Infect Dis* 2005; **41**:217–224.
15. Havlir D, Cheeseman SH, McLaughlin M, Murphy R, Erice A, Spector SA, *et al*. **High-dose nevirapine: safety, pharmacokinetics, and antiviral effect in patients with human immunodeficiency virus infection.** *J Infect Dis* 1995; **171**:537–545.
16. Chokephaibulkit K, Plipat N, Cressey TR, Frederix K, Phongsamart W, Capparelli E, *et al*. **Pharmacokinetics of nevirapine in HIV-infected children receiving an adult fixed-dose combination of stavudine, lamivudine and nevirapine.** *AIDS* 2005; **19**:1495–1499.