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Paediatric antiretroviral treatment programmes in sub-Saharan Africa: a review of published clinical studies

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Abstract

Knowledge of the experience and outcomes of current paediatric antiretroviral treatment (ART) programmes in sub-Saharan Africa can inform new programmes in the region as well as enhance existing ones. This is urgently needed to facilitate the scale-up of treatment, which is needed to address the burden of paediatric HIV cases on the continent. We reviewed the characteristics and outcomes of programmes with clinical paediatric ART studies published prior to 1 January 2008. The outcomes of the studies were comparable to similar ones from developed countries; however, the duration of follow-up was relatively limited in almost all the studies reviewed. One-year survival probability was between 84% and 91%, and considerable improvement in the clinical, immunologic and viral status of the paediatric patients was generally recorded. Loss to follow-up was less than 10% in all but two studies. Adherence to treatment was good and few adverse events were reported. This is despite the fact that many programmes were subject to enormous constraints in terms of health services, and despite widespread use of adult fixed-dose combinations for paediatric patients, including young infants. While the majority of children commencing ART were severely ill, most children were old (median age > 5 years for almost all studies) with relatively few infants and young children (age < 2 years) receiving treatment. This is in contrast to knowledge of rapid disease progression in the majority of HIV-infected infants and despite the World Health Organization's recent recommendations to commence ART in all HIV-infected infants less than one year old. There is an urgent need to address barriers to ART for infants. Studies of the outcomes of programmes treating infants as well as those with longer-term follow-up are also needed.

Keywords

children; growth monitoring; HIV/AIDS; infants; mortality; programme assessment; survival; treatment issues; treatment practices; WHO guidelines

Introduction

The burden of paediatric HIV infections is greatest in sub-Saharan Africa, where as of December 2007 almost 90% of the world's two million HIV-infected children were living, with approximately 370 000 new paediatric infections having occurred in the preceding year (UNAIDS, 2008). In the absence of antiretroviral therapy (ART), HIV-related illnesses account for approximately 10% of childhood mortality across the continent and up to 50%

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childhood mortality in southern Africa (UNAIDS, 2006; Little, Thorne, Luo, Bunders, Ngongo, McDermott & Newell, 2007). ART is highly effective in reducing morbidity and mortality in HIV-infected children in the developed world; however, until very recently, its availability to children in Africa has been limited (Patel, Hernan, Williams, Seeger, McIntosh, Van Dyke & Seage, 2008). For example, according to the most recent available paediatric ART coverage estimates, in more than half of sub-Saharan African countries, less than 15% of children needing ART were receiving it at the end of 2006 (WHO/UNAIDS, 2006). Coverage was below 35% for the remainder of the sub-continent, apart from Namibia and Botswana (WHO/UNAIDS, 2006).

Encouragingly, access to ART for children in sub-Saharan Africa is increasing, with more than 2 500 facilities providing treatment and nearly 160 000 children receiving ART by December 2007 (WHO, UNICEF & UNAIDS, 2008). Nine of the ten countries in which the vast majority of HIV-infected children live are in sub-Saharan Africa, and access to ART in these countries increased dramatically between 2005 and 2007. For example, in South Africa, Kenya, Malawi and Zimbabwe, the numbers of children receiving ART increased 2.6 times, 3 times, 4 times and nearly 5 times in that period, respectively (WHO *et al.*, 2008). The corresponding total numbers of children on ART in those countries by the end of 2007 were 32 000 (South Africa), 15 000 (Kenya), 10 000 (Malawi) and 8 000 (Zimbabwe) (WHO *et al.*, 2008).

ART provision for children in sub-Saharan Africa —with its enormous health service constraints —needs to be tailored to local circumstances. Outcomes may also be different to those in the developed world due to different socio-economic circumstances and background burden of disease. Information from observational cohorts of children receiving ART in Africa is therefore vital to demonstrate programmatic issues, such as the nature of ART provision on the continent and the effectiveness of different models of care for children, as well as the outcomes of children receiving ART.

Since 2004, reports from isolated cohorts of children receiving ART in Africa have been published with progressively increasing frequency and greater numbers of children on treatment. To our knowledge, there is one published review of clinical studies in the medical literature demonstrating good outcomes, but with little emphasis on the characteristics of individual programmes (i.e. Sutcliffe, Van Dijk, Bolton, Persaud & Moss, 2008).

This study was funded by the International Epidemiological Databases to Evaluate AIDS (IeDEA) Southern Africa cohort collaboration. We aimed to review published paediatric ART clinical studies in order to contextualize future paediatric ART cohort analyses, assess the feasibility of ART for children in Africa, and inform context-specific guidelines on treatment for children, as well as highlight areas for additional relevant research.

Our specific objectives were to review the following:

- The characteristics of paediatric ART programmes, in terms of funding, user fees, ART eligibility criteria and regimens used;
- The characteristics o f patients at ART initiation across different programmes;
- Outcomes among children receiving ART, specifically vital status and retention in care, as well as clinical and laboratory outcomes in those who remained in care; and,
- Treatment durability and adherence.

Methods

We searched the literature through the PubMed database using the search terms 'antiretroviral children Africa' and 'antiretroviral' AND ('paediatric' OR 'pediatric') AND 'Africa.' Eligibility criteria were observational studies published prior to 1 January 2008 with a cohort including at least 25 children treated with three-drug ART and reporting on vital status outcomes. The children needed to be part of an observational cohort and not participants in an antiretroviral (ARV) drug trial. Data were extracted onto a standard form and summarised as described under the following subheadings.

Data on treatment programmes

Variables extracted from the studies included the number of facilities at which ART was provided, external funding sources, user fees, clinical care providers, availability of laboratory testing facilities, criteria used to determine patient eligibility for ART, and ART regimens used.

Patient characteristics at ART initiation

In addition to the age and gender profile of the participants in each study, disease severity was summarised using as many of the following measures as were reported: CD4 cell count and CD4 percentage (CD4%), anthropometric data reported as age- and sex-standardised z-scores, viral load, WHO clinical stage of disease, and opportunistic infections. The relationship of caregivers to the patients was also recorded.

Outcomes on ART

We extracted information on overall mortality and loss to follow-up (as defined by each study individually), and specifically mortality at one year in those studies where this was reported. We also noted changes in markers of disease severity, including clinical events, growth, immune and virological response. We describe treatment durability in terms of proportion of children requiring treatment changes and the reasons for this, and report on adherence for those studies where this was measured.

Results

Characteristics of the treatment programmes

Overview of the studies reviewed and their countries of origin—The characteristics of 18 studies (15 cohorts) that met eligibility criteria are shown in Table 1. Most (13 of 18; 60%) were reports from a single health facility, with three of the remainder being from multiple sites within a country and the other two being reports of the Médecins Sans Frontières (MSF) HIV programmes from multiple resource-limited countries (including non-African sites). Most reports are from southern Africa and East Africa (see Figure 1). The Malawi Paediatric Antiretroviral Treatment Group (2007) reports on national aggregate cohort data, not individualized outcomes. Two studies were reported by each of the following programmes: Agence Nationale de Recherches sur le SIDA, Abdijan, Cote d'Ivoire (i.e. Fassinou, Elenga, Rouet, Laguide, Kouakoussui, Timite *et al.*, 2004;Rouet, Fassinou, Inwoley, Anaky, Kouakoussui, Rouzioux *et al.*, 2006); Red Cross Children's Hospital, Cape Town, South Africa (i.e. Eley, Nuttall, Davies, Smith, Cowburn, Buys & Hussey, 2004;Eley, Davies, Apolles, Cowburn, Buys, Zampoli *et al.*, 2006), and the MSF multi-site cohort (i.e. O'Brien, Sauvageot, Zachariah & Humblet, 2006;O'Brien, Sauvageot, Olson, Schaeffer, Humblet, Pudjades *et al.*, 2007).

Funding and payment—Sixteen of the 18 studies report on funding sources, and 15 of these received external funding for the ART programme in addition to state health-service resources. The most common funders were the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) and the Global Fund to Fight AIDS, Tuberculosis and Malaria (contributing to 25% and 31% of the studies, respectively). Eight studies acknowledged additional support for research activities.

Only McCord Hospital (in Durban, South Africa) did not provide free care and ART for HIV-infected children; rather a standard co-payment of approximately US$10 per month (irrespective of number of consultations, treatment or laboratory testing needed) was required per family receiving care (Reddi, Leeper, Grobler, Geddes, France, Dorse *et al.*, 2007). However, the provision of laboratory testing as part of routine care varied widely in the programmes reviewed. Outside of South Africa and the research settings, viral-load testing was not provided, and in some of the Malawian studies CD4 testing needed to be paid for by the patients (e.g. Ellis & Molyneux, 2007).

Providers of medical care—Half of the studies provided information on the main providers of medical care. Doctors are the exclusive providers in four of nine (44%) studies, and doctors provided care in combination with clinical officers and/or primary care nurses in another four of nine studies (44%). In a single study from Zambia, the focus for care provision was specifically from nurses and clinical officers (i.e. Bolton-Moore, Mubiana-Mbewe, Cantrell, Chintu, Stringer, Chi *et al.*, 2007). This was an explicit strategy of 'task shifting' aimed at extending the reach of HIV services and the programme successfully provided care to 4 975 HIV-infected children (2 938 on ART) via primary healthcare (PHC) facilities. This contrasts starkly to most of the other studies from hospital-based settings. Indeed, most studies that did not report on which cadre of staff provided clinical care are from hospital settings, suggesting a reliance on doctors.

Eligibility criteria for ART and the regimens used—Most of the studies used the World Health Organization (WHO) guidelines (e.g. WHO, 2004 and 2006) available at the time (or a local modification thereof) as criteria for ART commencement. Where ART was commenced prior to the publication of the 2003 WHO guidelines, the criteria in use were similar to those of WHO relating to clinical and/or immunological disease severity. In three studies, from Zambia and Malawi, access to virological testing to confirm diagnosis in children age ≤18 months was extremely limited, so presumptive diagnoses were made and treatment commenced in children with severe clinical and/or immunological disease (Bolton-Moore *et al.*, 2007; Ellis & Molyneux, 2007; Malawi Paediatric Antiretroviral Treatment Group, 2007). Ellis & Molyneux (2007) noted that in Malawi CD4 testing had to be paid for by the patient, so immunological eligibility criteria could only be considered in those who could afford testing.

The main first-line ART regimens used are shown in Table 2. Notably, four studies exclusively used adult fixed-dose combination (FDC) tablets.

Patient characteristics at the start of ART

Considering the 18 studies reviewed, a total of 7 477 children commenced ART, with the median (IQR) number per study being 236 (Interquartile range: 79–381). Gender representation was essentially equal, with females comprising 49.1% of the total cohort.

Age—The median/mean age of the children ranged from 4.2 to 9.2 years, in all except two studies. One of these specifically included only children aged 18 months to 5 years (i.e. O'Brien *et al.*, 2007), while the median age of 1.9 years for the Cape Town cohort (i.e. Eley

et al., 2006) was markedly younger than all the others. Where age categories are reported, it is clear that there are few infants and young children (age <2 years) on ART. Less than 12% were under 18 months old in all studies— except in one study each from South Africa and Mozambique, where 50% and 22% of children, respectively, were under age 2 years (Eley *et al.*, 2006; Marazzi, Germano, Liotta, Buonomo, Guidotti & Palombi, 2006). Overall, approximately 9.5% (650 of 6 777) of children in all cohorts of those studies reporting age category were under age 18 months.

Disease severity—The majority of children had severe disease at ART commencement (Table 1). In most studies more than 70% of children had advanced clinical HIV disease (WHO stage 3 or 4, or CDC category C) and their median/mean weight-for-age (WFA) and height-for-age (HFA) z-scores were well below 0. Only three studies provided data on weight-for-height (WFH) z-scores, with medians between −0.6 and −1.64. The median CD4% was below 10% in all but two studies, both of which included relatively larger numbers of young children (i.e. Eley *et al.*, 2004;Bolton-Moore *et al.*, 2007). Indeed, in the Zambian cohort, median CD4% declines with increasing age at the start of ART (Bolton-Moore *et al.*, 2007). Similarly, the proportion with CD4% <15% is high (≥79%) in all studies except those including many young children (i.e. Eley *et al.*, 2006;Marazzi *et al.*, 2006). Only seven of the 18 studies report on baseline viral load, indicating poor access to this technology, and the median/mean $\log_{10}$ viral load ranges were high. Studies from the Northern Cape Province (South Africa) and from Mozambique reported 80% and 55% of children having >5$\log_{10}$ viral load, respectively.

Seven studies reported on current or past opportunistic infections at the start of ART. Prevalence of TB at entry into the programme was 33% in Durban, South Africa (Reddi *et al.*, 2007), and 46% in Dodoma, Tanzania (Blé, Floridia, Muhale, Motto, Giuliano, Gabbuti *et al.*, 2007). The Tanzanian cohort, however, comprised a small group of institutionalised children and it is unclear whether TB was 'active' or previous. Other studies, from Zambia, Malawi and Côte d'Ivoire, reported lower proportions (6–7%) of active TB at commencement of ART, with previous TB in 13–24% of the children (Fassinou *et al.*, 2004; Bolton-Moore *et al.*, 2007; Bong, Chen, Jong, Tok, Hsu, Schouten *et al.*, 2007). Nutritional/gastrointestinal illnesses, fever, recurrent pneumonia and dermatitis were not uncommon.

Caregivers

Two studies from South Africa and one each from Malawi and Kenya reported on the child's main caregiver (i.e. Eley *et al.*, 2004; Reddi *et al.*, 2007; Ellis & Molyneux, 2007; Wamalwa, Farquhar, Obimbo, Selig, Mbori-Ngacha, Richardson *et al.*, 2007). This caregiver was the mother for between 38% and 79% of the children, with the greater proportion occurring in the studies that included younger children. Fathers were the primary caregivers for up to 21% of children in some studies, but for far fewer children in other settings (e.g. Eley *et al.*, 2004). Grandparents (mostly grandmothers) and other family members comprised the third-most-common primary caregivers, respectively providing care for 6–21% and 7–26% of children. Only 2–7% of the children were cared for by an institution.

Response to ART

Survival and retention in care—In all but four studies less than 10% of the children died during the follow-up period, with a maximum of 15.4% deaths in the study with the highest mortality (see Table 3). Loss to follow-up was also low (<10% in all but 2 studies). One-year survival probabilities are only reported by six studies and are all within a small range (0.84–0.91) (Figure 2). In general, lower probabilities of survival are seen in those studies where children were younger at commencement of ART.

Response to treatment in survivors

Clinical events—Fassinou *et al.* (2004) reported decreased incidence of pneumonia and diarrhoea after commencement of ART in children age <6.5 years from Cote d'Ivoire, with no change in older children, while Wamalwa *et al.* (2007) showed reduced hospitalisation during the six months after initiation of ART in a Kenyan programme. However, in that cohort, 58% of the children had been hospitalised during the six months preceding the start of ART.

Growth—The most consistent observation regarding growth in the 12 studies that reported this is improvement in weight-for-age (WFA) z-scores and/or reduced proportions in underweight, with the latter being reduced by 30–80% (Eley *et al.*, 2006; Marazzi *et al.*, 2006; Ellis & Molyneux, 2007; O'Brien *et al.*, 2007). Improvement in weight-for-height (WFH) z-score (reduced proportion with wasting) also appears consistent across the studies, with the proportion wasted reduced to a similar degree (cf. Eley *et al.*, 2006; Ellis & Molyneux, 2007). There is conflicting data with regard to height response: three studies showed improvement, albeit smaller than for other growth parameters, while three studies showed no change. It appears that while significant improvements in all growth parameters do occur after commencement of ART, it is rare for these to normalise.

Immune response—The median/mean increase in CD4% at 12 months was between 11% and 17.5% (Table 3). Rouet *et al.* (2006) found CD4% to increase during the first 18 months on treatment and then stabilise, with better immune recovery in those children on Nelfinavir as compared to Efavirenz-based regimens. Nyandiko, Ayaya, Nabakwe, Tenge, Sidle, Yiannoutsos *et al.* (2006) similarly found CD4% to increase rapidly during the first 30 weeks of ART, after which increases were much less pronounced.

Virological response—Ten studies reported on virological outcome at varying time intervals (see Table 3). This is a relatively high proportion as viral monitoring is not routinely available in sub-Saharan Africa outside South Africa and Botswana. At one year, the proportion of children with suppressed viral load (<400 copies/ml) in most studies was between 70% and 80%, but it was strikingly lower in the Côte d'Ivoire cohort at 49% (Fassinou *et al.*, 2004). The Côte d'Ivoire cohort was the only one reporting on viral suppression beyond one year, with approximately half the children being suppressed at both age 24 months and age 36 months (Fassinou *et al.*, 2004;Rouet *et al.*, 2006).

Treatment changes, adverse effects and failure—No studies reported specifically on the criteria used to ascertain treatment failure; however, 13 studies reported the proportion of children requiring treatment changes due to failure, toxicity or other reasons. Changes due to toxicity were minimal (<10% of children) in most studies, except the Zambian cohort where single drug substitutions were required for 17.6% of the children. Reasons for these substitutions, however, included toxicity and dosing issues (Bolton-Moore *et al.*, 2007). There were few adverse events reported in the six studies providing this data. Most common were skin rash, hepatotoxicity and anaemia. Two cases of Stephens-Johnson Syndrome occurred overall, one of which was fatal (Marazzi *et al.*, 2006; Bolton-Moore *et al.*, 2007). Switching treatment regimes due to failure was extremely rare (<5% in all studies that reported it) being highest in the Côte d'Ivoire cohort, with extended follow-up as expected (Rouet *et al.*, 2006). This is in strong contrast to the proportion of children with viral suppression in that study by Rouet *et al.* (2006).: 50–70% throughout follow-up.

Adherence—Adherence to ART was measured in eight cohorts, mostly by self-report alone (four studies). Supplementary pill counts were used in two studies, while pill counts and drug pick-up information were the primary instruments for one study each. Overall,

adherence was good, with significant interruptions (more than two missed doses per month) noted for less than 11% of children in any cohort.

Discussion

This review demonstrates overwhelmingly the feasibility and effectiveness of providing ART to children in sub-Saharan Africa despite enormous health-service and socio-economic constraints. Dramatic improvements in survival, and clinical, immune and virologic status were achieved. It is difficult to make valid comparisons with studies from the developed world due to differences in socioeconomic context, prior treatment experience, criteria for treatment initiation, ART regimens, and access to laboratory testing and specialist care (Patel *et al.*, 2008). For example, while viral suppression rates of 70–80% in most of the cohorts with access to viral load testing were certainly at least as good as, if not better than, those from rich countries, this may be due to the relatively older age of the children commencing ART and the fact that most children in Africa are treatment naïve (Van Rossum, Fraaij & De Groot, 2002). Nevertheless, it is notable that the good outcomes seen in these studies are similar across a range of settings, including those with limited access to ART drugs and laboratory technology as well as those where ART is not provided by doctors and care is administered from PHC facilities (such as in Zambia and Malawi) (see Bolton-Moore *et al.*, 2007; Ellis & Molyneux, 2007; Malawi Paediatric Antiretroviral Treatment Group, 2007). However, this review also highlights numerous aspects of the nature of current ART delivery in Africa, as described in the following sections.

Follow-up duration, mortality and retention in care

Due to the relatively recent availability of ART for children in Africa, follow-up periods are generally short, and long-term outcomes are as yet unexplored (except in the single small cohort from Côte d'Ivoire) (Rouet *et al.*, 2006). Nonetheless, most deaths occurred within the first few months after commencing ART, thus estimates of mortality are not likely to increase significantly, at least in the medium term. This is supported by the single longer-term study reported by Fassinou *et al.* (2004) where at 42 months there were no deaths additional to those reported at 12–24 months (Rouet *et al.*, 2006). Still, low mortality estimates should be viewed with caution in the five cohorts where short-term loss to follow-up (LFU) equaled or exceeded mortality (i.e. O'Brien *et al.*, 2006; Nyandiko *et al.*, 2006; Bolton-Moore *et al.*, 2007; Ellis & Molyneux, 2007; O'Brien *et al.*, 2007), as many of those classified as 'LFU' may have been deceased (Maskew, MacPhail, Menezes & Ruel, 2007; Krebs, Chi, Mulenga, Morris, Cantrell, Mulenga *et al.*, 2008). It is notable that all except one of the studies with this limitation were from multi-site collaborations, suggesting that it may be easier to have definite outcome ascertainment within a single site— as these may have specific patient-tracing and follow-up systems in place, or else may have made a concerted effort to ensure outcome ascertainment for the purposes of publication. Notwithstanding this, LFU in children in Africa is far lower than that of adults (Stringer, Zulu, Levy, Stringer, Mwango, Chi *et al.*, 2006). Interestingly, two cohorts (from Tanzania and Kenya, respectively) reported zero deaths and very low (3.4%) LFU (Blé *et al.*, 2007; Song, Jelagat, Dzombo, Mwalimu, Mandaliya, Shikely & Essajee, 2007). Both of these were small cohorts (59 and 29 children, respectively). The first was a residential institution for orphaned HIV-infected children with a medical doctor on site daily, while the second, in addition to providing free ART, also provided transport re-imbursement to the clinic attendees.

Age at ART initiation

The overall low mortality reported by the studies reviewed also needs to be viewed in context of the children being relatively old at the start of ART, with less than 10% overall

initiating treatment before 18 months of age. In contrast, we know that HIV disease progression to death or advanced disease occurs in 50% of perinatally HIV-infected children by age 2 years (Little *et al.*, 2007). Many infants and young children in Africa clearly need but are not receiving ART. Indeed, ART-treated children in Africa represent a cohort of survivors with relatively slower progression of disease, and good outcomes are to be expected. It is not surprising that the study reporting the highest percentage of deaths after one year on treatment (15.6% mortality) is from a tertiary institution, with over 50% of that cohort having been less than age 2 years at ART commencement, and 99% of the children having advanced disease (Eley *et al.*, 2006). Yet, even in this group of very ill children, mortality on ART was relatively low.

A number of factors explain the fact that in these studies children generally commenced ART at older ages than in developed countries (Patel *et al.*, 2008). First, this reflects the difficulty in diagnosing HIV infection in children under 18 months old where access to virologic testing is limited (Bolton-Moore *et al.*, 2007; Ellis & Molyneux, 2007; Malawi Paediatric Antiretroviral Treatment Group, 2007). This is also a consequence of poor access to appropriate ART formulations for children and the difficulty in dosing young children even where liquid formulations and refrigeration are available, due to the requirement for surface-area dosing. In fact, in Malawi, the site of three of the cohorts, all children were treated with split doses of the adult fixed-dose combination (FDC) Triomune (d4T/3TC/NVP) according to weight bands (Bong *et al.*, 2007; Ellis & Molyneux, 2007; Malawi Paediatric Antiretroviral Treatment Group, 2007), while one of the multi-country MSF cohort studies had the specific aim of demonstrating feasibility and good outcomes with use of adult FDCs in children (O'Brien *et al.*, 2006). . While the Malawian studies highlight the problems of dosing the smallest children (<8 kg) with tablet once daily (which is not recommended, as d4T should be given twice daily: (WHO, 2006), Ellis & Molyneux (2007) argue that the good outcomes reported support use of this regimen due to the benefits of low cost, availability and simplicity.

Many clinicians feel inadequately trained for the perceived complicated care of the very young (Eley & Nuttall, 2007; Meyers, Moultrie, Naidoo, Cotton, Eley & Sherman, 2007). In fact, the Malawian ART scale-up programme specifically treated young children only in health facilities where paediatricians or medical doctors skilled in paediatric care were available (Ellis & Molyneux, 2007). In South Africa, paediatric care, particularly of young infants, remains centered in tertiary-care institutions (Eley & Nuttall, 2007; Meyers *et al.*, 2007).

The relative lack of young children receiving ART in Africa may also be an indication of the poor integration of HIV services for children and shortage of prevention-of-mother-to-child-transmission (PMTCT) programmes and general child health services, which although they clearly have overlapping target patient groups, are often run as separate vertical programmes within the health system. This may result in poor systems for detection and referral to ART care for HIV-infected infants and young children before disease progression. Many children with HIV infection are only diagnosed once they are severely ill, or die before an HIV diagnosis is made.

Severity of illness at ART initiation

Despite the relatively old age of children in these studies (age > 5 years) and the fact that they represent survivors with slower disease progression, most children in the total cohort were severely ill at commencement of therapy. At least half of the children commencing treatment had advanced clinical disease and the median CD4% at ART initiation was low. This is in keeping with the use of WHO guidelines for treatment eligibility by most programmes. However, in the multi-country MSF cohort, the final CD4% after one year

remained lower in those with greater baseline immune suppression, suggesting that immune recovery may be limited if treatment is delayed until illness is advanced (O'Brien *et al.*, 2007).

It has been suggested that the background burden of disease in Africa may exacerbate disease progression in HIV-infected children and thus complicate ART. In this regard, it is notable that two studies reported very high prevalence of TB at entry into the programme (i.e. Blé *et al.*, 2007; Reddi *et al.*, 2007). However, those figures may have been over-estimates. The difficulty of making a definitive diagnosis of TB in children, particularly when dually infected with HIV, may lead to over-diagnosis to avoid missed opportunities to treat a potentially curable opportunistic infection. Nevertheless, a high prevalence of TB in children is cause for concern. The medication burden and potential for TB immune reconstitution inflammatory syndrome (IRIS) may complicate ART (Smith, Kuhn, Coovadia, Meyers, Hu, Reitz *et al.*, 2009). Furthermore, where lopinavir/ritonavir is used in the first-line regimen for young children, concomitant TB therapy requires additional ritonavir-boosting of the regimen. Notwithstanding, in Malawi, there was no difference in survival between children commencing ART with active TB, previous TB or a non-TB diagnosis (Bong *et al.*, 2007); however, only Nevirapine (NVP) -based regimens were used, and ART was delayed until the continuation phase of TB treatment to avoid Rifampicin–NVP interactions and the risk of IRIS. (Bong *et al.*, 2007).

Treatment durability

Treatment was well-tolerated with few adverse effects overall and few drug substitutions required. The rate of switching to second-line regimens was very low. This, however, needs to be viewed in the context of many of the cohorts not having access to virologic testing and/or second-line medication for children, as well as there being no current virologic guidelines for switching therapies in children (WHO, 2006). It is clear that a number of children are being maintained on first-line therapy despite ongoing viraemia, and the effects of this need to be examined in the long term. Furthermore, it would be useful to determine whether access to virologic testing has any implications for programme outcomes.

Growth response to treatment

Growth response as measured by scores for weight-for-age (WFA) and weight-for-height (WFH) was consistently good, despite probable poorer access to food in developing-country contexts, with very few programmes providing nutritional supplementation (Marazzi *et al.*, 2006). Still, the failure to attain normal z-score values for these parameters may reflect the residual insult of advanced disease. This is possibly also the reason for conflicting measures for growth response in terms of height-for-age (HFA), a reflection of chronic illness.

Representativeness

An important limitation of this review is that these studies may not be representative of all routine programmes across Africa. Although all are observational cohorts, many are from research settings, where care, monitoring, access to drugs and laboratory testing may be markedly better than what is available in routine services. The relatively high proportion of studies with follow-up information on patients' viral load supports this. In addition, there is a probable publication bias in favour of successful programmes; hence, the restriction of this review to published clinical studies may have selected programmes with better outcomes. It is plausible that country-level data, programme reports, and social-science literature may portray a different picture. Furthermore, all but one of the cohorts reporting on funding had received some form of external support in addition to that from state health services, albeit through the national programme in some cases. Nevertheless, two of the studies reported on the outcomes of routine national programmes (i.e. Malawi Paediatric Antiretroviral

Treatment Group, 2007; Jooste, Van Zyl, Baker, Crawford & Jassen, 2008), with one using only routinely collected data, yet their findings are consistent with those from research settings.

In addition to financial programme support, there was evidence of considerable international academic collaboration within these studies. While one-third of these published studies have both local senior and lead authorship, in an almost equal proportion (five of 16), both these roles are taken by international academics, and all except four of the publications (three cohorts) included at least one international collaborator. It is therefore possible that patient care at these sites may have been enhanced through the involvement of research institutions from wealthy countries, and thus may not be replicable on a massive scale. This also demonstrates the need to develop research and analytic capacity in sub-Saharan Africa so that lessons learned can be disseminated.

Conclusions

The feasibility and benefits of ART provision for children in sub-Saharan Africa have been clearly shown in a range of settings; however, infants and young children remain largely excluded from ART programmes, and commencement of ART occurs mostly in older children with advanced HIV disease. Emerging evidence of rapid progression of disease in children failing PMTCT regimens, and the survival benefit with early initiation of ART, has led to the revision of WHO guidelines to recommend ART commencement for all HIV-infected children under age 1 year (Mphatswe, Blanckenberg, Tudor-Williams, Prendergast, Thobakgale, Mkhwanazi *et al.*, 2007; Violari, Cotton, Gibb, Babiker, Steyn, Madhi *et al.*, 2008; WHO, 2008). There is an urgent need both to address barriers to the care of young children with HIV infection and to acquire a better understanding of the outcomes for children on ART and the determinants in this group.

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Biographies

Mary-Ann Davies is a registrar in public health, with an interest in paediatric HIV and TB. She has been involved with the antiretroviral treatment programme at the Red Cross Children's Hospital in Cape Town, South Africa.

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Olivia Keiser has a master's degree in biology. She was the epidemiologist in the data centre of the Swiss HIV Cohort Study. Currently, she is doing research towards a PhD, comparing treatment approaches and outcomes of HIV-positive patients in high-income and low-income countries.

Andrew Boulle is a public health specialist with an interest in the routine monitoring of HIV-treatment interventions. Since 2002, he has worked closely with the Khayelitsha and Western Cape Provincial antiretroviral treatment programmes in South Africa.

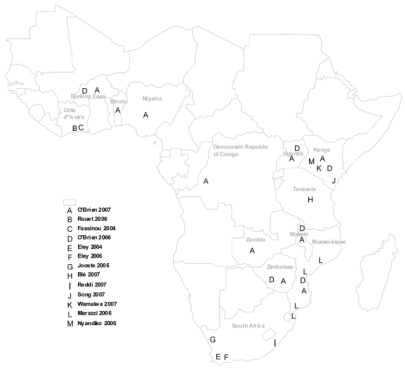

Figure 1.
Map of paediatric ART sites with published studies included in the review

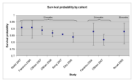

Figure 2.
Summary of survival probability as reported by nine paediatric ART studies from sub-Saharan Africa

Table 1

Summary of the studies reviewed and the characteristics of the children at the start of antiretroviral therapy (ART) for each cohort (CD4% = CD4 percentage; IQR = Interquartile range; WAZ = Weight-for-age z-score; HAZ = Height-for-age z-score; NR = not reported)

Study	Country	No. of sites	Observation time	No. of children on ART	Percentage females	Median (IQR) age (years)	Percentage aged <18 months	Median (IQR) CD4%	Percentage CD4 <15%	Percentage advanced stage[a]	Median (IQR) WAZ score	Median (IQR) HAZ score	Median (IQR) log viral load
Fassinou *et al.*, 2004	Côte d'Ivoire	1	2000–2002	78	44	7.2 (0.7; 15.2)[b]	5[c]	8.0 (1.9; 11.1)	NR	13	−2.02	2.03	5.4 (3.3; 7.0)[b]
Rouet *et al.*, 2006	Côte d'Ivoire	1	2000–2004	78	44	6.5 (0.7; 15.2)[b]	NR	7.5 (2.1; 11.1)	NR	NR	NR	NR	5.4 (5.1; 6.0)
O'Brien *et al.*, 2006	8 countries	multiple	2001–2005	1–184	48	7 (4.6; 9.3)	1	NR	85[d]	39	NR	−2.0 (−3.2; −1.1)	NR
O'Brien *et al.*, 2007	14 countries	26	2002–2006	568	45	3.2 (2.5; 4.1)	0	NR	79	42	NR	NR	NR
Eley *et al.*, 2004	South Africa	1	2002–2003	80	39	4.2[e] (3.5; 4.9)[f]	NR	NR	NR	94	NR	NR	NR
Eley *et al.*, 2006	South Africa	1	2002–2005	409	44	1.9 (0.7; 4.5)	51[c]	11.7 (7; 17.3)	66	99	−2.17 (−3.09;−1.12)	−2.51 (−3.41;−1.72)	5.6 (5.1; 6.1)
Jooste *et al.*, 2005	South Africa	>1 throughout province	2003–2004	100	NR	5.5[e] (0.3; 13)[b]	NR	NR	96	NR	NR	NR	NR
Nyandiko *et al.*, 2006	Kenya	9	2002–2005	279	49	6 (0.4; 13.7)[f]	7[g]	10 (1; 38)[b]	NR	NR	−2.6 (−9.6; 2.3)[f]	−2.4 (6.1;−4.2)[f]	NR
Marazzi *et al.*, 2006	Mozambi que	6	2002 ?	297	NR	5.1[b] (3.2)[h]	22[c]	NR	56	NR	NR	NR	NR
Blé *et al.*, 2007	Tanzania	1	2002–2005	59	34	4.5 (0.6; 10.6)[b]	5[g]	9.6 (0; 27.6)[b]	NR	NR	−2.13 (−5.49; 2.65)[b]	−2.07 (6.09;−4.37)[b]	NR
Reddi *et al.*, 2007	South Africa	1	2003–2005	151	51	5.7 (0.3; 15.4)[b]	NR	7.4 (2.1; 13.7)	80	70	−1.9 (−3.6; 0.9)	−2.2 (−3.0; 1.1)	NR
Song *et al.*, 2007	Kenya	1	2003–2004	29	47	8.5[e] (3.4)[h]	0	NR	NR	NR	−1.61[e] (1.39)[h]	NR	5.1 [e] (0.7) [h]
Wamalwa *et al.*, 2007	Kenya	1	2004–2005	67	49	4.4 (2.4; 6.0)	NR	6.2 (3.6; 10.3)	82	NR	−2.45 (−4.3; 1.54)	−2 (−3.32; 1.04)	6.4 (6.0; 6.6)[i]
Kamya *et al.*, 2007	Uganda	1	2004–2005	250	48	9.2[e] (4.5)[h]	NR	8.6 (3.5; 12.7)	NR	89	NR	NR	5.3[e] (0.8)[h]
Malawi Paediatric Antiretroviral Treatment Group, 2007	Malawi	Multiple throughout country	2004–2005	233	NR	NR	3[g]	NR	NR	NR	NR	NR	NR
Bolton-Moore *et al.*, 2007	Zambia	18	2004–2007	2 938	52	6.8 (3; 10.4)	10	11.8 (7.2; 17.4)	NR	72	−2.2 (−3.4; 1.2)		NR
Ellis & Molyneux, 2007	Malawi	1	2004–2005	238	46	7.3 (0.6; 17.6)[b]	12	NR	NR	86	−3.02 (−6.77; 0.69)[b]	−3.19 (−7.17; 0.99)[b]	NR
Bong *et al.*, 2007	Malawi	1	2004–2006	439	50	NR	2[g]	(0.1; 43.6)[b,j]	NR	NR	NR	NR	NR

[a] CDC category C disease, or WHO stage 3 or 4 disease.

[b] Range.

[c] Percentage among those less than age 2 years.

[d] CD4 percentage was only available for 34% of children and was only reported for children ≤59 months of age.

[e] Mean value.

[f] 95% confidence interval.

[g] Percentage among those less than age 1 year.

[h] Standard deviation.

[i] Children age 18 months to 3 years only.

[j] CD4 percentage given for different subgroups only, not for all patients in the cohort.

Table 2

First-line ART regimen used (FDC = fixed-dose combination; NRTI = Nucleoside Reverse Transcriptase Inhibitor; NVP = Nevirapine; EFV = Efavirenz; ; PI = Protease Inhibitor; 3TC = Lamivudine; d4T = Stavudine)

Main first-line regimen used	Study reference
Adult FDC d4T/3TC/NVP	O'Brien *et al.*, 2006; Bong *et al.*, 2007; Ellis & Molyneux, 2007; Malawi Paediatric Antiretroviral Treatment Group, 2007
2 NRTIs + NVP	Marazzi *et al.*, 2006; Nyandiko *et al.*, 2006; Bolton-Moore *et al.*, 2007; O'Brien *et al.*, 2007; Song *et al.*, 2007; Wamalwa *et al.*, 2007
2 NRTIs + EFV/PI	Eley *et al.*, 2004; Eley *et al.*, 2006; Fassinou *et al.*, 2004; Rouet *et al.*, 2006; Reddi *et al.*, 2007; Jooste *et al.*, 2008
2 NRTIs + NVP/PI	Blé *et al.*, 2007
2 NRTIs + NVP/EFV	Kamya, Mayanja-Kizza, Kambugu, Bakeera-Kitaka, Semitala, Mwebaze- Songa *et al.*, 2007

Table 3

Summary of the study outcomes (CD4% = CD4 percentage; IQR = Interquartile range; NR = not reported)

Study	Median (IQR) follow-up duration (months)	Number of children on ART	Percentage deaths	Percentage loss to follow- up	Percentage transferred out	Percentage treatment stopped or withdrawn	Percentage outcomes unknown	Median (IQR) CD4% gain at one year	Percentage viral load <400 copies/ml at one year
Fassinou, 2004	21[a]	78	11.5	NR	NR	NR	NR	NR	49.3
Rouet, 2006	36 (30–42)	78	11.5	NR	NR	NR	NR	15.6[e]	46.5[e]
O'Brien, 2006	6 (2–12)	1 184	3	8	0	0	3	NR	NR
O'Brien, 2007	14 (7–20)	568	6	8	4	2	1	16 (11–22.6)[f]	NR
Eley, 2004	NR	80	8.8	5	0	1.3	0	NR	75[h]
Eley, 2006	12[b]	409	15.4[d]	4.6 [d]	11.2 [d]	2.9 [d]	0 [d]	NR	69.7
Jooste, 2005	6[b]	100	9[d]	3[d]	1[d]	3[d]	0 [d]	NR	67[h]
Nyandiko, 2006	8 (7–10)[c]	279	3.6	11	0	0	0	11[a]	NR
Marazzi, 2006	10 (5–16)	297	9.5	4.2	0	0	0	NR	46[h]
Blé, 2007	12[b]	59	0[d]	0[d]	0[d]	0[d]	0[d]	15[a] (10.3–19.7)[c]	NR
Reddi, 2007	8 (4–14)	151	8.6	0	0	0	0	16.2 (9.6–20.3)	80.3
Song, 2007	15[b]	29	1[d]	3[d]	0[d]	0[d]	0[d]	NR	55[i]
Wamalwa *et al.*, 2007	9 (3–15)[j]	67	9	lR	NR	NR	NR	11.3	67[h]
Kamya *et al.*, 2007	12[b]	250	5[d]	1[d]	0[d]	0[d]	0[d]	14.7;11.3[g]	74
Malawi Paediatric Antiretroviral Treatment Group, 2007	12[b]	233	13[d]	9[d]	6[d]	0[d]	0[d]	NR	NR
Bolton-Moore *et al.*, 2007	12 (5–23)	2 938	6.7	13	5.4	0	0	14[a] (13.4–14.7)[c]	NR
Ellis & Molyneux, 2007	6[b]	238	8[d]	8[d]	2[d]	0[d]	0[d]	NR	NR
Bong *et al.*, 2007	Variable up to 12 months	439	NR	NR	NR	NR	NR	NR	NR

[a] Mean value.

[b] Only includes children with specified number of months potential follow-up duration; all children who were not lost to follow-up, transferred out, or deceased were followed up for this duration.

[c] 95% confidence interval.

[d] Total percentage with given outcome in specified follow-up period.

[e] At 36 months.

[f] Children with baseline CD4 percentage between 5% and 15%.

[g] Children with and without viral suppression, respectively.

[h] At six months.

[i] At nine months.

[j] Range.