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Global Challenges in the Development and Delivery of Paediatric Antiretrovirals

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Abstract

By the end of 2006, compared with 28% coverage for adults, only 15% of children with HIV who needed antiretroviral treatment were receiving it. Major challenges in delivering treatment include the lack of paediatric antiretrovirals that can be dosed in small children and limited studies examining safety and efficacy for existing antiretroviral formulations. The high costs of treatment have been reduced through the use of generic, fixed-dose combination drugs. Evidence-based strategies for managing resistance and the scale-up of pharmacological trials for children in low- and middle-income countries are critical to the success and future development of paediatric antiretrovirals.

Keywords

Paediatric HIV; antiretroviral; fixed-dose combination; generic drugs

The first clinical trials of antiretroviral (ARV) use in HIV-infected children were published in 1988 [1,2]. Since that time there have been numerous studies addressing the development and efficacy of first-, second- and newer-line agents in adult patients. However, issues specific to paediatrics, such as studies of optimal dosing strategies and the development of child-friendly formulations have been less thoroughly addressed. Children continue to be under represented among those receiving ARV treatment, often due to limitations in clinical infrastructure, human resources and access to appropriate drugs [3]. Compared with 28% coverage for adults meeting international criteria for ARV treatment, only 15% of children who needed ARVs were receiving them by the end of 2006 [4].

UNAIDS estimates that the number of children under 15 years of age living with HIV/AIDS in 2007 was 2.1 million (1.9–2.4 million) [S1] (http://www.unaids.org, revised March 2008) [5]. This number continues to increase with 420,000 (350,000–540,000) [S2]annual new

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Teaser

Development of generic, paediatric antiretroviral formulations is facilitating expansion of global treatment, but gaps remain in coverage and the range of available and internationally-approved antiretrovirals.

infections [5]. An estimated 40% of all HIV-positive children needing treatment are less than 18 months of age, with the mean age of HIV-positive children at 2.3 years [6,7]. In 2006, United Nations (UN) member states agreed on the goal of providing "universal access to comprehensive (HIV) prevention programmes, treatment, care and support" by 2010 [4] (http://www.unaids.org). To keep up with this agenda for children, greater attention must be focussed on paediatric treatment issues.

In a ten-year multicentre US cohort study, 70% of children were started on ARV treatment, a striking difference with overall global coverage, which was associated with large reductions in mortality (adjusted hazard ratio 0.24; 95% CI 0.11 – 0.51) [8]. A UK/Ireland cohort showed similar reductions in mortality (adjusted hazard ratio 0.05; 95% CI 0.03 – 0.1) and progression to AIDS (adjusted hazard ratio 0.2; 95% CI 0.2 – 0.4), with 63 % of the cohort on ARVs [9]. Data from other countries have demonstrated that similar improvements can be achieved in resource limited settings, where treatment is generally initiated at later stages of disease than in the developed world [10–12]. Notably, mortality rates in these cohorts were highest in the period immediately following the start of ARVs, due in part to malnutrition and baseline severe immune suppression [10,11,13]. With greater evidence supporting early treatment for all HIV-infected infants [14], more children will need feasible and age-appropriate treatment options than before.

Major challenges in delivering treatment include the lack of paediatric ARV formulations that can be dosed in small children and limited studies examining safety and efficacy for those that we do have. In contrast to adult studies, paediatric studies often enrol smaller numbers of patients, which also limits the interpretation of the available data. Drugs for HIV-positive children continue to be 'therapeutic orphans' [15] and paediatric ARVs that are safe, tolerable, efficacious and simple to use are urgently needed in resource-limited settings [6].

Paediatric ARV Treatment

First-line Regimens

The goals of first-line paediatric regimens include availability, efficacy, safety, durability and tolerability, while retaining a future second-line regimen when treatment failure occurs [16]. In accordance with the 2006 WHO guidelines for initiation of ARV treatment, first-line regimens generally include the use of two nucleoside reverse transcriptase inhibitors (NRTIs) and one non-nucleoside reverse transcriptase inhibitor (NNRTI) [17]. A 2006 survey of ARV use in 23 resource-limited countries representing >65,000 children reported that 30% were on a combination of zidovudine, lamivudine and nevirapine (AZT+3TC+NVP), 14% on stavudine (d4T) with 3TC+NVP, 3% on AZT+3TC and efavirenz (EFV), and 2% on d4T+3TC+EFV. In total, 49% of national paediatric centres surveyed had children on WHO-recommended first-line NNRTI based therapy [17]. Less than 1% utilised alternative regimens and 50% did not report paediatric specific data in this survey.By contrast, the 2006 Medicins Sans Frontiers (MSF) cohort of 3,754 [S3]children on first-line regimens, had 74% taking d4T+3TC+NVP, with fewer children on AZT+3TC+NVP (16%), d4T+3TC+EFV (8%) and AZT+3TC+EFV (2%) [18,19]. These studies reflect the range of first-line regimens used in resource-limited settings.

Second-line Regimens

Recommendations for second-line regimens are to include three new drugs, with one or more from a new ARV class [20]. When resources are available for genotyping, ARV selection is based on resistance profiles. WHO recommends abacavir (ABC) and didanosine (ddI) with a protease inhibitor (PI) such as ritonavir (r)-boosted lopinavir or saquinavir/r for empiric second-line treatment [20]. However, there are limited paediatric data available to show how

this NRTI/PI combination compares with optimal regimen sequencing when information from resistant genotypes is used, or how it impacts time to subsequent treatment failure. Moreover, there are few available, generic second-line formulations, making choices for second-line agents after failed first-line therapy even more difficult.

Impact of Treatment

There is growing experience with and efficacy evidence for paediatric ARV treatment in resource limited settings. Similar to findings in adults, the highest mortality rates among children occur soon after starting ARVs. In the largest published paediatric cohort, including almost 3,000 children on ARVs in Zambia, 57% of deaths occurred within 90 days of starting treatment [10]. However, children who survive beyond this early period have achieved sustained clinical, immunologic, and virologic improvement [10,21–23]. South African [24], Thai [25] and Cambodian [21] cohorts have demonstrated 69.7%, 76% and 81% viral suppression (<400 copies/ml) at 1, 1.4 and 2 years of follow-up, respectively. In the Zambian cohort, children experienced a doubling of CD4 percentage from 12.9 to 27% at 12 months of therapy [10]. An eight-country cohort from MSF studied 1,184 children who were started on an adult fixed-dose combination (FDC) of d4T+3TC+ NVP [19]. Similar CD4 improvements were reported, with additional benefits including weight gain, reduction in opportunistic infections, and improved quality of life. These studies confirm that children in low- and middle-income countries can achieve similar treatment efficacy to their counterparts in higher-income countries [23].

The majority of these children were treated with adult FDC tablets that were split to approximate paediatric doses [26]. Achieving acceptable, sustained drug levels for all components of an FDC is critical to achieving virologic suppression and treatment success. Of particular concern is achieving adequate levels of NVP in children who have variable capacity for hepatic drug metabolism as they mature. In a Thai study of 34 children taking split adult FDCs (d4T+3TC+NVP - GPOvir, Government Pharmaceutical Organization, Thailand) [26], NVP dosing was prioritised to achieve 120–200mg/m^2 every 12 hours with the goal to reach serum concentration levels of >3.4μg/ml, levels that have been associated with long-term virological response in adults [27]. Thirteen children received GPOvir as a first-line regimen and, of these, 92% had an undetectable viral load (<400 copies/ml) at 6–18 months of treatment when tablets were split in increments of at least one-half [26]. By contrast, when quarter-tablets of adult FDCs were administered to children in Malawi and Zambia significant under dosing of NVP was observed [28]. WHO guidelines now advise against splitting tablets into less than one-half to reduce the risk of inappropriate dosing [20].

ARV Procurement and Production

Agencies such as the Global Fund to fight Malaria, AIDS and Tuberculosis, the Elizabeth Glaser Paediatric AIDS Foundation, the Clinton HIV/AIDS Initiative partnership with UNITAID, the US President's Emergency Plan for AIDS Relief (PEPFAR), among others are increasing their commitment to the procurement and provision of paediatric ARVs. The Clinton/UNITAID agreement signed in November 2006 prioritised facilitating procurement of paediatric ARVS, resulting in a 40% reduction in their price. Following these negotiations, treatment for a 10 kg child using generic paediatric FDCs was estimated at US $60 per year or US $0.16 per day [29]. By the end of 2007, an estimated 100,000 additional children will have commenced ARV treatment through this partnership. By guidance from the MSF updated reports Untangling the Web [30] and WHO reports on actual prices paid for ARVs in the Global Price Reporting Mechanism [31], competitive pricing is modelled and communicated, enabling national programs access to more affordable paediatric ARVs in low- and middle-income countries.

To further this success, access to generic paediatric FDCs must be expanded. These drugs are essential tools for simplifying drug procurement, treatment (including more accurate weight-based dosing) and adherence. The high costs of treatment have been reduced in resource-limited settings through the distribution of generic drugs produced in countries including Brazil, India, South Africa and Thailand. The development of these generic paediatric FDCs occurs within a complex regulatory framework. After a decade of negotiations, the World Trade Organisation (WTO) introduced the Trade-Related aspects of Intellectual Property rights (TRIPS) agreement in 1994 to safeguard the intellectual property and exclusivity rights of pharmaceutical inventors [7,32]. Protection of pharmaceutical patents provides financial incentives for innovative research and development to occur. However, the WTO has acknowledged that this must be balanced against the urgent public health need for disease-specific medicines in low- and middle-income countries. Recognising the various stages of development of intellectual property regulations in each country, the WTO agreed to a staggered introduction of compliance with the TRIPS agreement between 1995 and 2005, with extensions granted until 2016, to enable these countries the opportunity to develop intellectual property legislation. During this period, increased advocacy and improved longevity with ARV treatment highlighted concerns regarding the impact of the TRIPS agreement on global availability of ARVs. In 2001, the WTO issued a ‘waiver’ to prioritise public health over intellectual property regulations. This waiver, known as the Doha Declaration, has enabled the ongoing production and distribution of generic ARVs for HIV-infected people in the developing world through TRIPS-encompassed flexibilities including voluntary and compulsory licenses [7,33,34]. In this context, development of paediatric-specific ARV formulations continues to occur.

Generic Drug Assessment and Approvals

Along with a regulatory framework, an independent review process was required to assess medication quality. In partnership with other UN agencies, the WHO introduced their prequalification program in 2001 to assist international organisations and governments to access drugs and diagnostics of acceptable quality, assessed via product data and inspection of manufacturing sites (http://www.who.int/prequal/). ARVs that receive prequalification approval are listed on the WHO Essential Medicines List [35], enabling procurement of medications of high quality and documented bioequivalence. A parallel system was developed by the FDA in 2004 (http://www.fda.gov) to facilitate purchase of generic ARVs by US government programs for distribution in PEPFAR-supported countries. Like the WHO prequalification program, the FDA’s tentative approval program asserts that a generic product meets safety, efficacy and manufacturing quality standards.

Both the WHO and the FDA systems have facilitated the global distribution of quality-controlled ARVs. However, few paediatric formulations have been reviewed or approved by either agency. By March 2008, of the 62 first-line generic options that the FDA has approved, 15 are in a paediatric dosing range, including two FDCs [36]. Of the 99 WHO prequalified first-line generic options in March 2008, 19 are in a paediatric dosing range [35]. To expedite the review and procurement of these drugs, MSF developed their own process to internally validate generic ARVs through the MSF Qualification Scheme (http://www.accessmed-msf.org). They have approved several dual- and triple-combination paediatric FDCs, now in use in MSF sites around the world.

Paediatric FDCs

d4T+3TC+NVP Triple Combinations

Paediatric FDCs are essential in maximising the effectiveness of first-line therapy and maintaining adherence [20]. With the UN goal of providing ARVs to all those in need by 2010 along with greater financial commitments, the paediatric FDC market is growing rapidly [7].

The life expectancy of children living with HIV is also increasing due to improved access to ARVs, and the number of HIV-positive children will continue to expand as the population of children and adolescents on treatment ages [37,38]. However, a challenge in obtaining WHO or FDA approval is the relative lack of pharmacokinetic data for these drugs. The first published data on the use of paediatric-specific FDCs will be from the Phase I/II CHAPAS 1 trial, where investigators have assessed the pharmacokinetics of a d4T+3TC+NVP combination in Zambian children (Triommune Baby and Junior, Cipla, India, Table 1) [39]. In this study, 71 children aged three months to 14 years were dosed according to weight bands, with six children excluded due to poor adherence. Of the 65 completing the study, 37% were female, 37% weighed <15 kg and most were malnourished according to Z-scores. The d4T and 3TC pharmacokinetic parameters were similar to adults, while NVP dosing resulted in higher concentrations and greater variability despite aiming for daily doses of 300–400 mg/m^2. In comparison to an earlier study using Triommune adult FDCs in which 18% of children had a sub-therapeutic random NVP level only four children (6%) on the paediatric FDC had sub-therapeutic C_{12h} levels (<3.0 mg/l). There was no increase in toxicity reported for children with higher levels. Although this study included children in six weight bands from 3–30 kg, only two children weighed less than 6 kg, limiting the ability to generalise data for this group.

This initial pharmacokinetic study will be followed by adherence, pharmacokinetic analysis in children weighing less than 6 kg and an assessment of the impact of malnutrition on all three active component trough levels. These are the paediatric FDCs that were granted FDA tentative approval in September 2007 and were consequently given WHO prequalified status (http://www.who.int/prequal/).

Pilot Phase I/II data on the pharmacokinetics of another d4T-based paediatric FDC (GPOvir-S7, GPO, Thailand, Table 1) in Thai children aged six months to 13 years have recently been presented and are similarly promising [40]. GPOvir-S7 was found to be therapeutically adequate in crossover studies of eight children in Phase I and 30–44 children in Phase II studies, weighing more than 6 kg. The primary study objectives, to compare the bioavailability of GPOvir-S7 with individual liquid drug formulations and NVP levels to an adult therapeutic concentration, were both met. Results of a larger multicentre pharmacokinetic study of this formulation will be available in 2008 (http://www.ClinicalTrials.gov Identifier NCT00312091).

Emtri Junior (Emcure, India, Table 1) has been formulated as both a dispersible FDC tablet and syrup. Baseline prospective data on 21 patients aged between six months and 10 years ranging in weight from 4.2–13.9 kg have also recently been published [41]. Investigators reported an increase in CD4 count along with weight gain, decreased incidence of fever, diarrhoea, infections and hospitalisations. However, no pharmacokinetic or adverse event information was included.

Other d4T-based paediatric FDCs in use include Triviro LNS Kid and its double-strength version (Ranbaxy, India, Table 1). Bioequivalence studies have been conducted in healthy adults, but no pharmacokinetic data are available for children. These FDCs havealready been internally approved for use in MSF sites but have not yet been approved by the WHO or the FDA (http://www.accessmed-msf.org).

Dual Combination ARVs

Manufacturers have been developing d4T+3TC combinations that have been formulated at two levels for smaller and older children (Table 1), although data at this point in time are limited. These drugs can be used during the lead-in period when starting NVP, and in combination with other ARVs. None have been submitted for prequalification review, and currently there are no available AZT+3TC paediatric dual combinations.

AZT-based Triple Combinations

There are two AZT-based triple FDCs in development for children. Avocomb-N Kid (Ranbaxy, Table 1) has been submitted for WHO prequalification review and could be commercially available in 2008. GPOvir-Z30 (GPO, Table 1) is limited to research use in Thailand, with pharmacokinetic studies planned for 2008.

Limitations of Currently Available Triple-FDCs

There are several challenges when using the d4T+3TC+NVP combination FDCs. These include the risk of early NVP resistance when it is used in a treatment regimen soon after exposure to single-dose NVP as part of prevention of mother-to-child transmission interventions [37,42–44], rifampicin-mediated induction of cytochrome P450 metabolism causing reductions in NVP levels in children who are under concomitant therapy for tuberculosis [45,46], the development of lipodystrophy with prolonged use of d4T [47] and the limited available data for using these FDCs in children weighing less than 6 kg. The multi-site Pediatric AIDS Clinical Trials Group (PACTG) 1060 trial is an ongoing study addressing the risk of virologic failure in infants previously exposed to NVP. Further safety data are also needed in children who are being started on ARV treatment early in life, hence at lower weights.

In 2006, WHO convened an expert working group to determine optimal concentrations of single- and multi-drug paediatric ARV formulations. Many of the currently available generic FDCs do not follow the recommendations of their recent draft report [48]. For example, neither the already approved Triommune nor the recently studied GPOvir-S7 were compounded in the WHO target strength of d4T 7mg+3TC 50mg+NVP 55mg [49]. Active partnerships between drug manufacturers and treatment implementers can help facilitate future drug development and prevent delays in external review processes.

Second-line Regimens and Beyond

As in adults, children will eventually fail treatment if viral suppression is not or cannot be sustained. Although experience with managing ARVs is accumulating, there is a limit to how long even an aggressively managed, highly durable regimen will last. In Botswana, about 16% of children were on second-line regimens after three years of treatment [50]. In a Thai cohort, after 192 weeks of a d4T-based regimen, 16% had virologic failure [51]. The November 2007 FDA approval of a lower strength version of ritonavir-boosted lopinavir (Aluvia, Abbott, USA) offers another dosing option to those countries who can afford to use this protease inhibitor for second-line regimens (http://www.biospace.com/news_story/). The nucleotide reverse transcriptase inhibitor tenofovir (Viread, Gilead, USA) is becoming an increasingly important option for adult first- and second-line treatment, but it is difficult to use in children due to problems with splitting the adult tablet and toxicity concerns [52]. A generic version of tenofovir (Matrix, India) was tentatively approved by the FDA in November and prequalified by the WHO in December 2007, which will allow greater access to the drug (http://www.who.int/prequal/). Studies are currently underway to evaluate a lower strength “sprinkles” formulation by Gilead that would facilitate more accurate paediatric dosing.

Recent innovations in ARV development are unlikely to be translated to paediatric care in resource-limited settings in the near future, but a number of studies are examining optimal dosing and clinical efficacy. Pharmacokinetic data for the fusion inhibitor enfuvirtide (Fuzeon, Roche, Switzerland) are available for children >6 years of age, but the drug requires twice-daily injections, making it difficult to use in children in general and raising concerns over injection-related side effects [53]. Early results of a Phase I pharmacokinetic and dose assessment study of the NNRTI etravirine (TMC125, Tibotec, USA) demonstrated comparable levels to those in adults [54] A Phase II ritonavir-boosted tipranavir (Aptivus, Boehringer

Ingelheim, Germany) study in children and adolescents has reported 48 week data on safety and efficacy, showing virologic and immunologic improvement in 115 heavily pre-treated children and adolescents [55]. This open label dosing study included patients with a median of six previous ARVs, 49.6% of whom had genotypic protease inhibitor resistance. Viral suppression (<50 copies/ml) was achieved in 35% of patients at 48 weeks. The pharmacokinetics, safety and tolerability of the integrase strand transfer inhibitor raltegravir (Isentress, Merck, USA) is currently under study in Phase I/II trials in children and adolescents. (http://www.ClinicalTrials.gov Identifier: NCT00485264). A Phase II study of ritonavir-boosted darunavir (Prezista, Tibotec, Belgium) in children >6 years old is also ongoing (http://www.ClinicalTrials.gov Identifier NCT00355524). In order to make these drugs available in resource-limited settings, and in formulations that make it possible to dose in children, manufacturers, funders and programmes need to work together and prioritise paediatric treatment needs.

Summary

Paediatric ARV treatment has been successful when implemented with consistent supplies of high-quality drugs in the context of clinical and social support for children and their families. Unfortunately, this has not been the reality for most of the world's children living with HIV. Treatment expansion will require increased development of child-sized drugs that are formulated to deliver to infants and children (e.g. through dispersible tablets). Dosing schedules should optimally be based on pharmacokinetic and clinical outcome studies that take into account how nutrition status (e.g. by weight-for-age Z-score) impacts tolerability and response to treatment. Another key challenge is increasing the availability of quality-controlled generic drugs that national programmes can afford. Two paediatric FDCs (Triommune, Cipla) were approved by the FDA and WHO for the first time in August 2007 and there are more drugs under review. Although currently available paediatric FDCs were not created to follow WHO's recent recommendations for optimal ARV formulations, these recommendations can guide manufacturers seeking to develop new paediatric ARVs. In December 2007, WHO launched "make medicines child size," a global campaign to improve availability and access to paediatric-specific drugs, including ARVs (http://www.who.int/childmedicines/en/) that will help focus needed resources on reaching this goal.

In order to provide children with a lifetime of HIV treatment, evidence-based strategies for sequencing regimens with appropriate paediatric formulations are needed. The expansion of pharmacological trials for children in low- and middle-income countries is ongoing and essential to the future development of paediatric ARVs. With greater focus on paediatric HIV treatment and more FDC options, children have a better chance of being able to keep pace with the global ARV scale up.

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Table 1

Generic Paediatric Antiretroviral Fixed-dose Combinations (FDC)

Trade name[1]	FDC[2]	Concentration	Manufacturer
Dual combinations			
Coviro-LS Kid	d4T+3TC	5 mg+20 mg	Ranbaxy, India
Coviro-LS Kid DS	d4T+3TC	10 mg+40 mg	Ranbaxy, India
Emduo Junior	d4T+3TC	10 mg+40 mg	Emcure, India
Emduo Suspension	d4T+3TC	10 mg+40 mg per 5 ml	Emcure, India
Lamivir S Baby	d4T+3TC	6 mg+30 mg	Cipla, India
Lamivir S Junior	d4T+3TC	12 mg+60 mg	Cipla, India
Triple combinations			
Emtri Junior	d4T+3TC+NVP	10 mg+40 mg+70 mg	Emcure, India
Emtri Suspension	d4T+3TC+NVP	10 mg+40 mg+70 mg per 5 ml	Emcure, India
GPOvir-S7[3]	d4T+3TC+NVP	7 mg+30 mg+50 mg	GPO, Thailand
Triommune Baby[4]	d4T+3TC+NVP	6 mg+30 mg+50 mg	Cipla, India
Triommune Junior[4]	d4T+3TC+NVP	12 mg+60 mg+100 mg	Cipla, India
Triviro-LNS Kid[5]	d4T+3TC+NVP	5 mg+20 mg+35 mg	Ranbaxy, India
Triviro-LNS Kid DS[5]	d4T+3TC+NVP	10 mg+40 mg+70 mg	Ranbaxy, India
Avocomb-N Kid[5]	AZT+3TC+NVP	60 mg+30 mg+60 mg	Ranbaxy, India
GPOvir-Z30[6]	AZT+3TC+NVP	30 mg+15 mg+28 mg	GPO, Thailand

[1] All drugs are in tablet form, unless otherwise noted.

[2] d4T – stavudine; 3TC – lamivudine; NVP – nevirapine; AZT – zidovudine.

[3] Phase I/II

[4] FDA tentative approval and WHO prequalified

[5] Under WHO review

[6] Phase I, 2008 (planned)