

What Strategies to Boost Production of Affordable Fixed-Dose Anti-Retroviral Drug Combinations for Children in the Developing World?

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Abstract: Background: No more than 8% of HIV positive children needing treatment in low- and middle-income countries have access to antiretroviral drugs (ARVs). Children presently account for about 4% of all treated patients, while for equitable access they should make up at least 13%.

Aims: This study explores key issues, implications and interaction dynamics to boost production of easy-to-use and affordable fixed-dose combination (FDC) ARVs for children in the developing world. Potentials for equitable solutions are examined including priority steps and actions, appropriate treatment options and reliable forecasting methods for paediatric ARVs, as well as combination incentives to generic companies against market unattractiveness and enforced intellectual property (IP) rights. Moreover, implementation strategies to enhance the development and production of affordable ARV paediatric formulations and appropriate supply systems to ensure availability are investigated.

Results: The current market for FDC paediatric ARVs is already substantial and will only grow with improved and scaled up diagnosis and monitoring of children. This provides an argument for immediate increase of production and development of FDC ARVs for children. These formulations must be low cost and included in the list of Essential Medicines to avoid children continuing to lag behind in access to treatment. Access-oriented, long-term drug policy strategies with the ability to pass muster of governments, the UN system, as well as generic and research-based enterprises are needed to let children gain expanded and sustained access to FDC ARVs. Under the requirements listed above, IP-bound Voluntary License (VL) flexibilities do appear, if coupled with substantial combination incentives to generic firms, as a fitting tool into the needs. Policies must consider enhancing human resource capacity in the area of caregivers and social and health workers aiming to spread correct information and awareness on effectiveness and rationale of FDC ARVs for children. Policies should urge that paediatric ARV treatment programmes entwine with extant interventions on prevention of mother-to-child transmission, as well as with HIV treatment initiatives focused on mothers and household members. Policies, again, should consider centralising functions and pooling resources to help overcome drug supply barriers. WHO's brokering role in VL-based agreements between wealthy and developing country industries, as well as its technical guidance in setting international standards should not be waived while looking for sustained access to optimised ARV treatments for children. Strategies discussed in this paper, while taking unavoidability of marketing and profit rules into account, look closely into the trade and drug policy directions of China and India according to frontier crossing implications of their IP management trends as well as their multi-faceted penetration strategies of both the wealthy and under-served markets the world over.

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STEPPING UP ACTION FOR CHILDREN TO BE INCLUDED IN APPROPRIATE ARV TREATMENT REGIMENS

Background

Twenty years into the epidemic, HIV/AIDS is having an increasing impact on the health and welfare of children. Recent estimates from UNAIDS suggest that globally there are 2.3 million children (1.7 – 3.5 million) less than 15 years of age living with HIV, close to 90% of whom reside in sub-Saharan Africa. In 2005 alone, an estimated 540,000 (420,000 – 670,000) children were newly infected [112], mostly through mother-to-child-transmission (MTCT).

HIV infection in children is having an increasing impact on child survival. In 2005, there were an estimated 380,000 (290,000 – 500,000) AIDS-related deaths in children under 15 years of age, out of total of 3.1 million HIV/AIDS-related deaths worldwide [5]¹. Approximately 330,000 of these deaths were in children living in sub-Saharan Africa, as opposed to a mere 200 by comparison in the industrialized world. While children represent just 6% of all people infected with HIV/AIDS as of December 2005, they accounted for 14% of the 3.1 million AIDS deaths in 2005. As a result of these staggering numbers, the contribution of HIV to under-five mortality in Africa rose from 2% in 1990 to approximately 4% in 2005 [116]. The contribution of HIV to child mortality in certain parts of Southern and Eastern Africa, however, ranges from 20%-50% in selected countries. Despite the magnitude of these numbers, it is still possible that HIV-attributable child mortality numbers under represent the actual situation because children with HIV have largely been ignored from national HIV agendas and rarely been counted.

A principal reason behind the significant contribution of HIV infection to childhood mortality is the aggressive course of illness in children, and the heightened levels of mortality in the absence of paediatric treatment, both in the form of antiretrovirals and cotrimoxazole prophylaxis to prevent opportunistic infections. With immature immune systems, rates of HIV disease progression in small children are accelerated considerably. Rates of progression to AIDS or death by age one have been reported ranging from 15 – 30% [105, 60, 97], up to 50% by age two, and 60 % by age five [79].

Access to HIV Antiretroviral Treatment

There has been considerable progress made in recent years in terms of access to antiretroviral treatment for HIV infection in low- and middle income countries. According to the most recent report from WHO on the progress of the 3 by 5 initiative which endeavoured to put three million HIV-infected individuals in low- and middle income countries on ART by the end of 2005, 1.3 million individuals in these countries are now on treatment, up from 400,000 just two years earlier. In addition, sub-Saharan Africa, the continent hardest hit by the epidemic, saw its share of people on treatment rise from 25% to 50% of world totals during that same time period. An estimated 250,000 to 350,000 deaths were

averted in 2005 alone because of access to lifesaving antiretroviral treatment [125].

Unfortunately, this increased access in treatment for so many is counterbalanced by lack of access for many others. Most recent data published in 2006 in the Bulletin of the World Health Organization put the number of individuals in need of treatment in low- and middle-income countries at 6.5 million which includes approximately 665,000 children under the age of 15. 270,000 of these children in need of treatment are under the age of 18 months and have special needs with respect to treatment [17]. Recent estimates put the number of children on treatment at about 52,000, or about 4% of all adults and children currently receiving treatment [112].

Scaling up access to paediatric ART has been hindered for numerous reasons, principally a lack of focus on HIV-infected children by many donors and national governments, limited capacity in country to treat children with HIV, higher costs of paediatric ART (often 50 – 90% more than adult versions for branded products) [62], lack of ARV formulations for use in children, particularly fixed dose combinations for children under the age of 12, a lack of appropriate strength tablets (many adult formulations are not scored), limited liquid formulations, a lack of paediatric labelling for many ARV drugs – particularly for infants, and difficulty gaining registration within countries. Even when ARV drugs have been labelled for children, they are often only appropriate for specific subsets of children such as those above a certain age or weight limit [62].

Global Commitments and Moral Imperatives

The global community has put forth numerous declarations and commitments to advance access to antiretroviral treatment among the HIV-infected community. These include:

- The **Millennium Development Goals** (MDG) which call for a two-thirds reduction in the mortality rate for children under five, and to halt and begin to reverse the spread of HIV/AIDS—by the target date of 2015.
- The **United Nations General Assembly Special Session (UNGASS) Declaration of Commitment on HIV/AIDS** called upon governments to improve access to HIV care, support and treatment. This declaration was followed up by a new resolution on **Universal Access** in October 2005 which called on governments to come “as close as possible to the goal of universal access to treatment by 2010 for all those who need it...”
- “**A World Fit for Children**”, emerging from the UN General Assembly’s first session devoted exclusively to children, and including over 70 heads of state and or government, issued a strong call to improve the lives of children. HIV/AIDS figures prominently as one of the four key priority areas for action.
- The **3 by 5** initiative, which called upon governments and donors to collaboratively work to place 3 million people on treatment by the end of 2005.
- The **G8 Declaration** issued in Gleneagles, Scotland in July 2005 called for addressing HIV/AIDS through

¹www.unaids.org/epi/2005/doc/EPIupdate2005_pdf_en/epi-update2005_en.pdf.

the whole continuum of care from prevention through treatment and care [53] as well as for universal access to ART for all by 2010 [46, 47]².

- **Unite for Children – Unite Against AIDS**, a global campaign launched by the UN Secretary General, UNICEF, UNAIDS and other partners, calls for placing 80% of HIV-infected children in need on ART by 2010.

Despite these commitments, HIV-infected children have until recently not figured prominently on the treatment agenda. Commitment is increasing, however. Major international organizations including UNICEF and WHO, national governments such as the United States' President's Emergency Plan for AIDS Relief (PEPFAR), foundations including the Clinton Foundation as well as many other international organizations including faith-based and academic institutions, are dedicating significant resources to increase the number of eligible children on treatment. The accelerated development of low-cost, generic, fixed-dose combinations has the potential for dramatically changing the landscape and ensuring that the goals listed in the declarations above and the priorities outlined by different organizations are met. While generic production of fixed dose combinations for children exists, it is limited to local use in a few countries such as Thailand. Dialogue with pharmaceutical companies has started, however, and the recently announced public-private partnership announced by the First Lady of the United States, Laura Bush, will be instrumental in fast tracking achievement of results in this area.

Treating Children with HIV – A Moral Imperative

There is a moral imperative to place children on treatment. Access to paediatric ART in the West has resulted in children born with HIV living healthy lives into and through their teenage years. In addition, several studies have demonstrated that it is possible to treat HIV-infected children in resource-constrained settings, and that children in these settings respond as well as do children in more resource-rich settings.

Fassinou *et al.* demonstrated high two-year survival rates among a cohort of 78 HIV-infected children in the Ivory Coast. The overall probability of survival was 72.8% at 24 months for children with < 5% CD4 cells versus 97.8% survival in children with ≥ 5% ($p < 0.01$). In addition, after an average 756 days on HAART, 50% of patients had undetectable viral load and the median CD4 percentage for all children receiving HAART was 22.5% [42].

In South Africa, Eley *et al.* conducted a study among 80 HIV-infected children, 75% of whom had severe clinical disease, severe immune suppression or both. For those who received ART for at least 6 months ($N=17$), 84% of the sample became clinically relatively well. Children receiving treatment experienced no severe drug reactions [37].

In Thailand, Puthanakit *et al.* studied the response to ART in a cohort of 107 children enrolled between August 2002 and July 2003. In patients receiving ART, the median CD4 cell percentage rose from 3% at baseline to 21% at 72

weeks. Also at 72 weeks, 76% of patients had HIV RNA levels of < 50 copies/mL [86].

Global commitments have spoken to the need to scale up treatment efforts, and studies have shown children respond well to treatment. With this background there is a moral imperative to treat children with HIV infection. To make this a reality, however, there is a need to push toward lower cost drugs, preferably in fixed-dose combinations that can be easily delivered within low-resource settings.

Paediatric HIV Formulations – The Current Reality

Despite global declarations and evidence of the effectiveness of paediatric ART in resource-constrained settings, scale up to the level of universal access has been limited despite the best intentions for a variety of reasons. These include:

- **Cost** - Paediatric drugs, while having decreased in cost significantly over the last year, still cost significantly more than adult formulations of the same drugs. In many parts of the world, twice as many adults could be treated with the same amount of funding. Further reductions in cost are made more difficult because children do not finance their own care and are therefore unable to advocate for themselves. In addition, generic drug manufacturers rely on economies of scale because of small profit margins. Without a large market, it is harder to compete [88]. Improved quantification methods can help provide a clear picture of the overall needs for treatment both at national and global levels, and strengthen the argument for ARV drugs appropriate for infants and young children.
- **Dosing issues** – Because of the lack of a full range of paediatric formulations, dosing becomes much more complex. Under or overdosing becomes more common in children because drugs are processed differently in this population and it is difficult to accurately take into consideration all the various factors to ensure appropriate dosing. In addition, because of a lack of uniformity of active agents in adult pills, merely dividing pills into halves or quarters does not ensure adequate dosing of the child [93]. In addition, although WHO recommends 3TC + d4T or AZT and either NVP or EFV as first line treatment, programmatic adherence to this recommendation is complicated for numerous reasons. These include: (1) D4T's liquid formulation requires refrigeration (and thus is inappropriate in many of the highest burden countries); (2) 3TC is only indicated for children over 3 months of age; (3) AZT has a low dose to volume ratio – older children have to consume large volumes to get proper dosage; (4) NVP cannot be used in conjunction with rifampicin for children with tuberculosis because of drug-drug interactions resulting in lower blood concentrations of NVP and hence underdosing; and (5) limited data on the use of EFV in children less than 3 years of age. Second line regimens are even more problematic in that they are often unpalatable, need cold storage, and have no generic equivalents [93].

²www.commissionforafrica.org/english/about/documents/06-07-06-05_ev_edinburgh_declaration.pdf.

- **Paediatric labelling** - Many available ARV drugs have not been tested or labelled for paediatric use; some that have been labelled are only suitable for limited subsets, such as for children above a certain age or weight limit. The Elizabeth Glaser Pediatric AIDS Fund (EGPAF), reports that only 12 of 20 AIDS drugs developed so far are labelled for paediatric use; and just 7 for children under the age of 2 [96].
- **Limited number of paediatric formulations**, especially fixed dose combinations. Combining different drugs in appropriate formulations is particularly complex for infants and young children, often resulting in under and overdosing, and making treatment unavailable for many children most in need.
- **Difficulty gaining registration** – to appropriately treat young children, it is necessary to get approval to sell all formulations of all necessary drugs within a country. Fixed dose combinations, particularly those referenced in national guidelines, are easier to register because there is clarity regarding need and intent to use.

Paediatric HIV Formulations – The Way Forward

Scale up of paediatric ART in resource-constrained settings will be greatly facilitated with the introduction of generic HIV formulations appropriate for children. Formulations for children should be made available in single dose, two-drug, and three-drug combinations to allow practitioners maximum flexibility and convenience in prescribing. Specific benefits to be achieved include:

- **Easier to administer.** Fixed dose formulations in various strengths are easier to administer because the difficulty inherent in calculating the correct dosage for different weight bands is removed. In addition, when treatment is available in fixed dose combination form, there is no longer the need to address combining different drugs, some of which must be halved and quartered, and others which must be administered in liquid form. This simplification leads to greater treatment adherence and improved clinical outcomes.
- **Reduction in the risk of under and overdosing.** The risks of under and overdosing are dramatically reduced as the appropriate proportion of the active ingredient has already been calculated and distributed throughout the drug.
- **Lower pill burden.** Adults with HIV infection are already benefiting from reduced pill burdens through the combination of different drugs into one pill. This has resulted in many patients taking one and the same pill morning and evening. This has in turn increased acceptability of pill taking and correspondingly has improved adherence.
- **Easier to procure and supply.** A major disadvantage of paediatric formulations for younger children is that they come in liquid formulations that take up considerable more storage space and have a shorter shelf life. Fixed dose combinations in tablet format will ensure less spoilage making procurement and supply easier, and will also require less storage space in local

pharmacies. Greater longevity also makes local pharmacists more willing to store the medications as they are less worried about losing unused stock.

- **Less expensive.** The introduction of generic fixed dose combinations for adults has generally resulted in lower costs. Paediatric formulations, generally more expensive than adult formulations, should become more affordable as fixed-dose combinations.
- **Standardization of ART without compromising effectiveness.** Scale up of paediatric ART has been hampered because of the complexity of prescribing paediatric ART. Standardization – combining all the necessary drugs into one formulation and making formulations specific to different weight bands – will make scale up much more achievable without compromising the effectiveness of the drugs.

Studies on the use of fixed dose combinations in children to date have demonstrated that this is an effective strategy. The results of a study utilizing divided adult fixed-dose combinations in Thailand was recently published (September 2005). Thirteen children received a fixed dose combination of Stavudine, Lamivudine, and Nevirapine (GPO-VIR) as their first-line regimen. Twelve of these 13 children had HIV RNA <400 copies/mL at 6-18 months, with a median increase of 216 in CD4 at 6 and 12 months. This study demonstrates that adult fixed dose combinations can be used effectively as an interim approach while waiting for a paediatric fixed dose combination drug formulation [25].

Similarly in Uganda, a study with Triomune (stavudine, lamivudine and NVP) involving 81 children resulted in significant improvements in CD4 and VL levels [9].

However, there are still concerns about breaking/cutting adult formulations to approximate a paediatric dose. This practice can easily lend itself to under- or over dosing, leading to the development of resistance and removal of other options from the antiretroviral armamentarium.

It will also be important to develop fixed dose combinations for oral suspension and solutions as well [96]. Approximately forty percent of all children requiring ART are under the age of 18 months. Many of these children will be unable to swallow pills, but can still benefit from all of the other advantages to be derived from fixed dose combinations including ease of administration, avoidance of under and overdosing, and greater possibility for scale up.

For scale up of paediatric HIV treatment to occur and for universal access to become a reality, it will be important that patents do not constitute a barrier to placing children on necessary treatment. Patent protection is provided for through the World Trade Organization's 1994 agreement entitled Trade Related Aspects of Intellectual Property Rights (TRIPS). However, to address the serious public health threat posed by HIV, some flexibility to TRIPS was included as part of the Doha Ministerial Declaration in 2001. The least developed countries belonging to the WTO have the option to postpone compliance with TRIPS until 2016.

Governments in countries with heavy HIV burdens also have the option of pursuing a policy of compulsory licensing under which they can allow generic drugs to be produced without the agreement of the patent holder. However, many

countries have been reluctant to pursue this approach because of fears of trade repercussions from major trading partners.

Governments of lesser developed countries with heavy HIV burdens should be supported if they choose to make use of the flexibilities outlined in the Doha Declaration. Patent holders should be commended for their recent increased flexibility to allow voluntary licenses for generic production of ARVs. If royalties are kept low, prices will not be overly inflated, thereby increasing access for all children in need [52].

Contribution from the Pharmaceutical Industry

Both innovators and generic manufacturers have played an important role in prolonging the lives of people living with HIV. Innovator companies, specifically, have conducted extensive research to develop these drugs that have resulted in prolonging the lives of millions of people worldwide.

The generic pharmaceutical industry has played an important role in making HIV ART more affordable in the adult population. During a span of 3 years from 1999 to 2002, competition from the Indian generic drug industry resulted in a reduction of prices from over \$8,000 per patient per year to under \$200 per year [16]. This has only just begun to be felt in the area of paediatric formulations [3]. Nevertheless, there is great opportunity to take a similar stand as they already have with the adult market to ensure that children receive equitable access to lifesaving drugs.

Promising Developments

There are several promising developments on the horizon. The United States, one of the largest providers of ART announced on March 13th, 2006 through First Lady Laura Bush that the US Government will lead an international public-private partnership with the goal of increasing the range of drugs available for treatment with children. The US Government will work with both innovator and generic pharmaceutical companies, as well as with UNICEF and UNAIDS to tackle barriers to effective treatment of children. High on the list of priority actions will include the development of paediatric formulations that are appropriate for resource-limited settings. Innovator companies that are expected to participate in this partnership include Abbot, Bristol Myers Squibb, Gilead Sciences, GlaxoSmithKline, Merck, and Pfizer. Generic companies expected to participate include Aspen, Pharmacecare, Aurobindo, Cipla, Emcure, and Ranbaxy, all of which have paediatric ARV development programmes.

PEPFAR has also committed itself to focusing more on the needs of HIV-infected children. In fiscal year (FY) 2004, PEPFAR supported pilot programs focusing on paediatric ART in several countries including Uganda, Namibia, Zambia, South Africa, and Botswana. These programs have been scaled up in FY 2005. In FY 2006, all emergency plan countries are slated to have programs supporting treatment of paediatric HIV/AIDS. Through the initiative, the numbers of children on treatment has increased dramatically in PEPFAR countries from 4,800 in September 2004 to 9,500 in March 2005, or 7% of total PEPFAR ART recipients [82].

Other developments have also taken place. The Clinton Foundation has negotiated significant price reductions for paediatric ART. These savings are available to all accessing these drugs through the Clinton Foundation. UNICEF is launching a paediatric fund to spur development and production of both diagnostics and ART appropriate for infants and young children. Advocacy organizations, including the Global AIDS Alliance have done much to raise global awareness of the needs of HIV-infected children. Regulatory agencies such as the FDA have agreed to put in place special provisions to fast track approval for paediatric ART formulations.

Conclusion

The numbers of children with HIV are growing rapidly, primarily in Sub-Saharan Africa. This is essentially a result of the failure of national governments and the international community to successfully implement PMTCT programmes – geographical coverage in most countries is low, and uptake at centres providing these services less than optimal. With immature immune systems leading to rapid onset of severe disease, poor mechanisms for early diagnosis, limited capacity for treatment, and few drugs appropriate for children, over half a million children a year are dying of HIV-related illnesses. Progress is being made to improve PMTCT coverage, policies and programmes to address early diagnosis are being implemented, and healthcare workers are being trained to manage the clinical needs of HIV-infected children. The greatest stumbling block that remains to be addressed is increasing the access of ARVs appropriate for infants and young children. The generic pharmaceutical industry can play a leading role in this endeavour.

ACTIONS TO PROMOTE PAEDIATRIC ANTIRETROVIRAL TREATMENT AS A CHALLENGE FOR DEVELOPING COUNTRIES HEALTH SERVICES: CONSIDERATIONS BASED ON THE CASES OF UGANDA AND ETHIOPIA

We intend here, through analysing the cases of Uganda and Ethiopia, to explore the issues related to the current implementation of ART (AntiRetroviral Treatment), in particular paediatric ART, in Sub-Saharan African Countries, a region struggling in the fight against HIV/AIDS and in reaching the Millennium Development Goals (MDGs) set for 2015 (Table 1).

The health situation in Uganda

Uganda has a population of 26 million, with a GDP (gross domestic product) per capita of 1500 \$. It ranks 150th according to the Human Development Index (HDI). The annual population growth is 4.4% [111].

Health Sector Financing

The financial resources currently allocated to the Health Sector are about 250 million USD and are mainly provided by external support (Budget Support and Projects). The revenues from cost recovery account for less than 10%. The annual health expenditure per person is about 9 USD.

The Ugandan Health Sector, and in particular the HIV/AIDS programmes [110] are actually funded through the following channels:

Table 1.

AIDS Epidemic, December 2005 – UNAIDS: GLOBAL/SUB-SAHARAN AFRICA/ETHIOPIA and UGANDA					
		Global	Sub-Saharan Africa	Ethiopia	Uganda
Adult HIV prevalence	Total	1.1 %	7.2 %	4.7 %	7.1%
Number of people living with HIV in 2005	Total	40.3 million	25.8 million	1.6 million	1.2 million
	Children <15 years	2.3 million	2 million	112,000	180,000
Number of new HIV infections in 2005	Total	4.9 million	3.2 million	262,000	>70,000
	Children <15 years	700,000	460,000	> 35,000	>10,500
AIDS deaths in 2005	Total	3.1 million	2.4 million	134,000	78,000
	Children <15 years	570,000	500,000	>25,000	
Children in need of ART				58,700	50,000

- i) The National Health Budget, including the resources coming from the external Budget Support.
- ii) Specific Projects, directly funded by different bilateral Cooperation.
- iii) Global Initiatives, such as the Global Fund to fight AIDS, Tuberculosis and Malaria (GFATM) and the PEPFAR (Presidential Emergency Program for AIDS Relief in Africa).
- iv) “Out of pocket” contribution from the patients (user fees), present in some departments of public hospitals and in Private not for Profit (PNFP) health facilities.
- v) Professional health insurance (civil servants and international companies) and community based health insurances (although increasing, the latter system is still little effective).

Despite the severity of HIV infection, AIDS ranks 4th as a general cause of mortality [19]. Malaria, respiratory infections and diarrhoea still account for 53% of the causes of mortality [19], with the greatest burden in the population under 15. Furthermore the data demonstrate that the Primary Health Care (PHC) system is still very weak.

HIV/AIDS Impact in Uganda: Prevention and Treatment

The prevalence of HIV infection in adults is 7.1% (end 2005). Since the onset of the epidemic, a cumulative number of over 2 million Ugandans have been infected with HIV [41]. According to the preliminary results of a seroprevalence study carried out in 2005, 10% of these (200,000) are children below 15 years. The number of children currently estimated to need ARV treatment, according to clinical and laboratory criteria, is approximately 50,000. Only 5,000 children (10%) are currently receiving ART, out of 65,000 patients currently under treatment in Uganda (Table 1). About 50 million \$, accounting for the 25% of the Ugandan government health budget, would be the annual cost of universal access to paediatric ART.

Uganda has managed to bring down the HIV prevalence of 20% in 10 years, thanks to a massive action of prevention and political advocacy. It is undoubtedly considered a success story, along with Thailand and Senegal. Although ARV treatment has been available in the country since 1998, the scaling up of treatment programmes started only recently, with support funds from global initiatives (GFATM, PEPFAR, Gates Foundation, Clinton Foundation etc.), from bi-

lateral and multilateral cooperation and with the National Health Sector Strategic Plan II (HSSP II, 2006 - 2010) targeting the provision of ART services in a big share of the country's health facilities [59, 102].

Criteria for Provision of Free-of-Charge ARV Drugs

Currently in Uganda, the need for ART dramatically overwhelms the resources available to provide this service. Criteria for prioritisation of access to free ART have been established: for prevention purposes the focus is on the prevention of mother-to-child transmission of HIV (PMTCT) and on the post-exposure prophylaxis (PEP, in case of accidental exposure for health workers or to rape victims). For treatment purposes the focus includes:

- i) HIV+ mothers identified in PMTCT programmes and to their HIV+ family members (PMTCT-Plus).
- ii) Children and infants infected by HIV through mother-to-child transmission, blood transfusion, sexual abuse or infected needles
- iii) HIV+ people already enrolled in care and support activities
- iv) HIV+ participants involved in health research projects for HIV/AIDS, whose access to ARV drugs is interrupted after completion of the research protocol.

The mean age of HIV+ children is 2.3 years. AIDS and related diseases are responsible for the deaths of 14,000 children each year (and at least one child dies due to AIDS-related illness every hour, every day [103]). 66% of children born with HIV will not reach their 3rd year and 75% will have died by the age of 5 years if not started on ARV treatment [83]. Despite the efforts done by the Government of Uganda and the Development Partners, even through the availability of considerable financial resources, there is still a big gap between the number of children who need ARV treatment and those who actually receive it. HIV infection affects child morbidity and mortality and the benefits of paediatric ART even in this context have not yet been realised.

ARV Treatment Opportunity for Children

The Ugandan “Health Sector Strategic plan 2006-2010” prioritises the scaling up of paediatric ARV treatment [4, 78]. Along with the Development Partners, the Ugandan Government elaborated strategies and policies to address the issue of HIV in children and achieve this priority objective. A “National Paediatric ART sub committee” has recently

been appointed, responsible for promoting Paediatric ARV treatment in Uganda through:

- i) The integration of the paediatric HIV/AIDS care into the national Integrated Management of Childhood Illnesses Algorithm
- ii) The integration of the paediatric ARV therapy into the comprehensive Health Care Guidelines for Uganda
- iii) The promotion of paediatric voluntary counselling and testing by introducing it into the Comprehensive Health counselling and testing. The Ugandan Ministry of Health has approved a plan for the expansion of PMTCT services and their integration with the ART facilities, utilizing free of charge ARV drugs: the development of this plan should cover the entire country within 5 years. In fact there is currently quite a large number of health facilities in the country involved in ART, mainly treating adult patients, while the coverage of paediatric ART at country level is still inadequate, limited to urban areas.

The Health Situation in Ethiopia

In terms of human development Ethiopia remains one of the least developed countries, ranking 179th out of 185 countries classified for HDI. Moreover the consistent increase in HIV infection in the country has to be taken into account. For example according to the official country data, the adult prevalence of HIV infection has reached 4.7% and as high as 7-12% according to other international sources.

Health Care Financing

Based on 2003 data the current annual pro-capita health expenditure is 5.6 USD, half of which is public health expenditure (including donors' support) while the other half is out-of-pocket expenditure by the patients. In order to achieve the MDGs, Ethiopia has to increase the amount of public resources allocated to its healthcare sector.

60% of public health expenditures covers recurrent costs (salaries, drugs, etc.), while the remaining 40% is for capital expenses (mainly constructions). However the government's budget (including the donors' contribution) allocated to the health sector is definitely higher than actual expenditures [35].

The sectoral evaluation jointly performed by the government and donors has underlined the insufficient absorption capacity by the government administration at the central and regional levels, mainly due to scarcity of human resources and procurement capacity. This situation makes it difficult for Ethiopia to achieve not only its national objectives but the health related MDGs.

The Impact of AIDS

In Ethiopia the adult seroprevalence for HIV was estimated at 4.7% (end 2005). This prevalence data, though relatively low if compared with many African Countries to its south, is really worrying if adequately considered within the country's social and demographical context. The country's epidemic is concentrated mainly in urban areas, and stabilised here, while a slow increase is registered in rural areas. The incidence of HIV in the younger age groups is increasing. In a country with over 70 million people, 85% living in

rural areas and with 64% under 25 years, the country prevalence is expected to rise. Ethiopia currently ranks 6th in the global list of countries, for total number of people affected by the disease, after South Africa, India, Nigeria, Zimbabwe and Tanzania, 5th in Africa).

The country response to the epidemic started in 1985 with a National HIV/AIDS Task Force, and was subsequently strengthened in 1987 with the establishment of the NACP (National HIV/AIDS Control Programme) within the Ministry of Health, committed in epidemiological surveillance and prevention activities. In 1998 the national AIDS policy was approved. Actually only in the last years the AIDS control programme has been given real importance, with the financial contribution provided by big external donors: GFATM, World Bank AIDS Programmes, PEPFAR, and the commitment of many bilateral cooperations.

In 2002 the HAPCO (HIV/AIDS Prevention and Control Office) was established, under the Prime Minister and recently passed under the Ministry of Health, with the role of Principal Recipient for the GFATM funds. The first GFATM funded programme in the country started in 2003 and has substantially contributed to foster the response to the epidemic, especially in terms of information and prevention.

In Ethiopia, according to the Federal Ministry of Health's Fifth Report of "AIDS in Ethiopia" (2005 estimates) the people living with HIV/AIDS is 1.591 million, 112,000 of which are children (<15). During 2005, 147,000 HIV+ pregnancies occurred with almost 40,000 new HIV infections among children and 25,000 deaths, and 29,000 new paediatric AIDS cases. The current estimates give figures of about 112,000 HIV+ children (0-14 years), with 63,000 in need of ART. The latest communication (January 2006) publicly given by the Federal Ministry of Health (FMoH) states that currently only 654 children are under ARV treatment in the whole country, out of both 58,000 in need of paediatric ART and a total number of around 22,000 currently treated patients. Over 50 million \$ would be needed (40% of the annual government health budget, 120 million) to realise the right to treatment for every child in need.

The Access to Paediatric ART

The analysis summarised above refers to the health context of two countries representing significant cases. Uganda was the first country in Africa to acknowledge the problem of HIV/AIDS and to face it, it's a "success story" with a still high but possibly decreasing prevalence. In contrast, Ethiopia has a lower but possibly increasing HIV prevalence. The country is less equipped to face the problem, because of later recognition of the epidemic and of its big population. From this analysis some important elements emerge about the challenges and constraints for the access to ART, and in particular to paediatric ART. They include technical, organisational, economic and equity barriers, as well as information, co-ordination and infrastructure gaps.

Actions and Recommendations

The strategies clearly identified and sustainable to face the problem of HIV/AIDS infection in children are, of course the HIV PMTCT and the early awareness and education in schools. However, on average in sub-Saharan Africa only 10% of pregnant women can access antenatal care. In analysing the official programme documents related to the consid-

ered African countries compiled at national and international levels (WHO, UNAIDS, UNICEF), a complexity of actions and recommendations can be assimilated but more as guidelines than as real programmes, because it is difficult to implement in the short term. It is vital to:

- 1) Ensure better access to ARV treatment for all children who need it especially in the rural areas. All the health facilities involved in the programme should be provided drugs and equipment for efficient paediatric ART and its clinical monitoring and follow up.
- 2) Verify the capacity of health facilities to implement the national / regional / district ARV protocols with respect to paediatric care, identify and address the gaps. The Ugandan Ministry of Health, through its Health Sector Strategic Plan II (HSSP II), aims to provide ARV treatment services by scaling up availability at all hospitals (92 in total) by 2007 and at 75% of Health Centre IVs (220 in total) by 2010, thus achieving the full country coverage.
- 3) Carry out comprehensive training in paediatric HIV care to all health care workers involved in HIV treatment and care of children in order to improve the quality of this complex service. Training should also be done for social workers and logistic – administrative staff in order to improve the overall management of ART programmes.
- 4) Improve laboratory services and expertise of lab technicians, in order to carry out baseline and follow up investigations, as well as diagnostic tests for children less than 18 months. This will help confirm the HIV status in approximately 50% of infected infants at or near birth, in 96% by the 28th day of life [35, 83].
- 5) Integrate preventive services (PMTCT) and ART services, thus reducing the new infection in children and providing timely ART to HIV+ mothers and children in need of it.
- 6) Standardise the paediatric drugs and formulations, reducing the number of different syrups and improving adherence. Improve drug procurement and distribution.
- 7) Scale up the Information, Education and Communication activities focusing on the benefits and results achievable through the correct ARV treatment in children.
- 8) Encourage family treatment approach and community involvement, in order to improve adherence and avoid drop-out and drug mismanagement.

The Role of the Private Sector [12, 15]

The role of the private health sector in the provision of HIV care is often overlooked by national programmes, as well as by development partners, although private health facilities perform a critical function in providing services for the diseases carrying stigma, such as Sexually Transmitted Infections (STIs) and HIV in many poor countries. Moreover there is evidence that where ARV drugs are available in the private market, there is the possibility of misuse of these drugs in an uncontrolled private health sector, with the risk of development of drug resistance.

Many countries have distributed national guidelines for ARV use and treatment protocols, but the difficult access to the public services often facilitates the proliferation of private practice, traditional practice, pharmacies that provide treatment without control and sometimes illegally. A study carried out on 21 private practices in Uganda revealed that only 4 physicians based their ARV prescription based on laboratory reports, for only 38 out of the 340 patients under treatment. Those lab examinations were paid 150-165 USD per patient. For example, in India, in a cohort of 200 HIV+ patients treated by private health facilities, only 10% of them had a good response to treatment, while 50% had interrupted the therapy and at least 80% had been given a wrong treatment with many different drugs, according to their availability on the private market.

The public sector definitely needs to have the lead in the provision of effective AIDS care. It often lacks the confidentiality ensured by the private sector, but is acknowledged as technically more reliable. The best strategy would be a collaborative involvement of the private health sector with special attention to quality of care and service coverage.

Importance of the Back Office [14]

Health System Strengthening is a crucial element for the achievement of the development target, including the MDGs, in African Countries. Particularly important are the functions and structures of a country health system defined as “back office”, usually overlooked by development and humanitarian actors. All the key components of a health system have to work in synergy in order to obtain sound results for the health status of the population.

Due to financial or visibility reasons, the development partners are often oriented at funding vertical programmes, creating severe distortion in the basic structure of the health services in the beneficiary countries. The renewed attention of the international community toward the health of the poorest population, fostered by the AIDS phenomenon, could constitute additional contributions needed for the strengthening of the health back office.

Cost Effectiveness Analysis [104]

A good use of resources is vital to improve the quality of life, especially for poor population in limited resource settings. Several studies have been carried out in order to provide policy makers with objective criteria for adequate decision making in public health, also in the view of achieving the MDGs within 2015.

One of those studies, carried out in sub-Saharan Africa and South-East Asia utilising as indicator the DALY cost (Disability Adjusted Life Year) in international \$, gives interesting and well documented results.

The study has obviously many limits, not being able to consider aspects difficult to measure, such as human rights issue, ethical criteria and real impact of each strategy on the population. For instance, the media campaigns for STIs prevention and the interventions targeted on sex workers are the most cost-effective activities for the health of the population. They do have a role, although often overlooked in comparison with other more complex and expensive strategies.

Many factors affect the priority setting in health. Some aspects of HIV/AIDS have to be taken into consideration that do not comply with cost-effectiveness criteria. Further studies are needed in these aspects. It's easy to conclude that ART should be provided always in combination with preventive strategies.

Finally, it's important to consider the potential benefits brought to the general health care system by the introduction of complex diagnosis and treatments.

Conclusions

With regard to the MDGs, the Less Developed Countries have evident and actual difficulties in achieving the minimal goals within the healthcare system set for 2015. Their health systems, still little developed, are sustained by development partners at least for 50% of their budget. In the current situation it is really difficult to cope with the high maternal and child mortality registered sub-Saharan Africa.

In this context some expensive programmes are being implemented, also promoted by the international attention targeted at vulnerable populations such as HIV+ children, orphans and poor families.

From the case studies reported above it seems that this effort could produce too little benefits for the targeted vulnerable people as well as for the whole population. In this regard some studies have analysed the impact of these programmes, their cost-effectiveness, the overload on fragile health care systems ill-equipped for the management of paediatric AIDS.

Possibly the resources committed for this needy population (big resources if compared with the global cost of health services in poor countries) would benefit the quality and accessibility of essential priority services such as obstetric care, children immunisation, diagnosis and treatment of malaria, use of rehydration salt for diarrhoea.

Decision making and prioritisation with regard to HIV/AIDS can not be based only on economic criteria. Political, ethical and human right issues have a determinant role.

There is sound evidence that many African Countries are definitely not ready for the complexity of ARV treatment. In the same time there is hope that the joint effort to upgrade their health systems for this complex task will strengthen the whole health sector.

The concern of the international community should focus on the right to health for these populations, and its actions should be consequential. The rich countries are still doing too little.

PREFERRED ARV TREATMENT OPTIONS FOR CHILDREN: MAKING SURE THE CHILDREN ARE NOT LEFT BEHIND IN TREATMENT SCALE UP

Key Considerations Within a Public Health Approach to ART for Children

The World Health Organization (WHO) promotes a public health approach to antiretroviral therapy (ART) to facilitate treatment access in resource-limited settings [124]. This is reflected in published guidelines for ART and use of ARV

drugs for prevention of mother to child transmission (PMTCT) [141], and now in the recently produced paediatric ART guidelines [136]³.

An extensive and expanding evidence base confirms that combination ART is effective in prolonging and improving the quality of life for HIV infected children, regardless of age of diagnosis, transforming HIV into a chronic disease [42, 67, 86]. Timely use of ART through maximal and durable suppression of viral load reduces HIV-related morbidity and mortality; improves quality of life; and restores and preserves immunologic function.

The WHO guidance for adults and children promotes selection of a simple and standard national first-line formulary of antiretroviral (ARV) medicines [11] that consolidates treatment options into two sequential potent regimens. For adults this shift led to a wide range of fixed-dose combinations becoming available, rapid and significant reduction in ARV prices by the end of 2005, and massive scale up of ART in resource limited settings (estimated 1.3 million people receiving ART by the end of 2005, approximately 5 % of whom are children) [140]. Treatment programmes and centres report good initial responses to the standard regimens [44]. However two major obstacles have prevented similar such progress being made for young children. Firstly the lack of technical and programmatic capacity to diagnose infection early in children, and secondly the lack of FDCs to be able to treat children under 5. Whereas some countries are beginning to be able to treat older children, younger children especially those under two years of age are not gaining access to ART treatment programmes.

The use of standardized simplified ART regimens are essential to the scale up paediatric ART. Countries need to identify and select a limited number of suitable, affordable, available first-line and second-line regimens to build then a limited ARV drug formulary. Standard first and second line ART regimens for children need to be selected and agreed upon at a national level. WHO provides preferred options for both first and second line therapy in its ART recommendations. These are based upon on the best available scientific evidence and seek to avoid the use of substandard protocols, avoid the potential for the emergence of drug-resistant virus, and offer a durable response that preserves future treatment options.

WHO recommends that countries select this standard first and second line regimen for use in public and private sector facilities. Other programme factors that need to be considered in establishing the national formulary and ART treatment guidelines for children include ability to treat all ages (i.e. consider including family focused care), the availability and suitability of drug formulations including, where possible, fixed dose combinations of ARV drugs (especially for use in those under 5 years or up to 14 kg of weight [57], licensing approval by national drug regulatory authorities for the products required and the recommended doses; toxicity profiles, laboratory monitoring requirements; potential for maintenance of future treatment options; anticipated patient adherence (including consideration of drug regimens taken by parents or carers, as appropriate); prevalent coexisting conditions such as malnutrition; other frequently occurring

³<http://www.who.int/hiv/pub/guidelines/whopaediatric.pdf>.

infections such as TB and possibly hepatitis B and hepatitis C in infants and children; varied HIV subtypes (e.g. HIV-2); drug procurement and supply capacity; and cost-effectiveness.

The concurrent use of three separate ARV medications is recognized to achieve the best possible suppression of viral replication and to arrest the progression of HIV disease. With three major oral ARV classes available, ART therapy is therefore built upon two sequential highly active ART regimens. Through expert consultation, initial consensus was achieved to recommend use of a non-nucleoside reverse transcriptase inhibitor (NNRTI) class, supported by a dual nucleoside reverse transcriptase (NRTI) backbone in first-line therapy for adults and children. This then reserves a potent new class, the protease inhibitors (PI) for use in second-line therapy. To this is added two new NRTIs (previously unused) to minimize cross-resistance: to enhance potency, ritonavir-boosted PIs are recommended. Adherence to any regimen (first line or second line) is required to improve treatment outcomes and limit the appearance of resistance. The actual choice of regimens would also need to consider a regimen with low total pill count and frequency of consumption, as minimizing these are proven methods of optimizing adherence. The existing triple and double FDC drugs provide clear advantages to supporting adherence and programme delivery.

Specific Considerations for Drug Formulations and Doses for Children

FDCs are the corner stone of ART in national programmes that have scaled up. While some child specific FDCs have been developed, none have yet been approved by stringent regulatory authorities. FDCs reduce the total pill burden which improves adherence which, in turn, limits the emergence of drug resistance and greatly simplifies ARV forecasting, procurement, storage and distribution logistics. For some adult ARV combinations once daily dosing has become available and this further simplifies drug regimens. The availability of combinations suitable for child remains unacceptable. Solid forms (this includes, granules, crushable tablets and capsules) are preferred for ease of use, but syrups and solutions do remain necessary to treat very young or very sick children who cannot swallow whole tablets or capsules. The range of currently available syrups and solutions have many shortcomings: they have high cost, present difficulties for dispensing and storage, have a reduced shelf-life, and for some drugs use unsuitable excipients (alcohol) and have very poor palatability. Health workers and care providers wishing to provide ART for children therefore face the difficult choice of breaking scored tablets, crushing tablets and dividing capsules because adapted paediatric formulations of ARVs are not available. For older children it is preferred to give solid formulations, and there are capsules and tablets of single ARVs in sufficiently low doses to enable accurate dosing for children. The pharmacokinetics of some crushed tablets or sprinkled capsule contents have been evaluated, and suggest acceptability and efficacy. Many of the currently available adult FDCs do not have all the drug components evenly distributed in the tablets, making splitting of tablets unsatisfactory. This lack of available formulations makes decisions by national drug regulatory authorities

on licensing products for use in children, as well as national programme decisions on which formularies to select, very difficult.

The prequalification programme has provided approval for 15 paediatric syrup drugs. To deliver first line treatment within national programmes simple reformulation of existing adult FDCs could contribute and should not require complex regulatory approval as clinical efficacy data for single drug use is already available and bioequivalence and stability are more easily demonstrated. The WHO working with paediatric ARV experts has already identified the following single dose and FDC drugs that would be required in reformulated forms and could significantly contribute to national scale up of treatment:

Scored Lower Dose Forms of:

- **lamivudine (3TC)**
- **zidovudine (AZT)**
- **abacavir (ABC)**
- **nevirapine (NVP)**

Scored FDC Formulations of:

- **AZT/3TC**
- **AZT/3TC/ABC**
- **AZT/3TC/NVP**
- **D4T/3TC/NVP**
- **ABC/3TC**
- **D4T/3TC**
- **Heat stable lopinavir/ritonavir tablets (Lop/r)**

Dosing information on efavirenz for children under 3 would enable a reduced dose form of this or similar once daily FDCs to be made.

While liquid formulations are available, they are very costly and often have special requirements and characteristics that may preclude their widespread use. They may require special storage requirements such as refrigeration (e.g. d4T). They may require large volumes of liquid to be dispensed at any one time [e.g. AZT (zidovudine)], to enable sufficient volume for use between clinic visits where transport is a challenge for patients. Where dispensing is undertaken monthly an average 10 kg child would need approximately 3-4 bottles of each drug (i.e. up to 12 bottles to take home after each visit). The PI class of drugs have high insolubility and are dissolved in large volumes of alcohol (e.g. ritonavir is dispensed in a 47% alcohol excipient) and have a very unpalatable taste. For national programmes calculations of required drug by site for shipment is very complex and the space requirements for storage and distribution are enormous.

Improving Use of Available ARVs

Given the realities of the available ARVs for children, using the adult FDCs and other single solid dosage forms of ARVs is the only available way to provide ART to children, while pressure is applied to originator and generic companies to address the gaps in the formulatory options. In reality, national programmes and national partners in care provision

such as MSF or other international NGOs have had to use adults FDCs for most children. The currently available evidence from Thailand [25], Uganda [9], and Malawi confirms that satisfactory short term virological and immunological benefits are seen in children receiving adult fixed-dose combinations of stavudine/lamivudine/nevirapine (d4T/3TC/NVP). However this is far from ideal, and it is important to note that pharmacokinetic studies in Malawian children confirm that the use of single-drug liquid formulations is better than splitting adult FDCs for smaller children [27]. However the splitting or crushing of adult-dose solid FDC ARVs may currently be the only available option that national programmes have to provide treatment of children in many resource limited settings. Recent work undertaken by WHO to determine optimal dosing options using adult FDCs confirms that current options do not provide for any safe treatment options for smaller and younger children (under 5 years). For most adult FDCs currently available it is not possible to determine safe dosing regimens for children under 11-14kg. This means that programmes have to rely upon syrups, solutions and other dosage forms.

While the use of tablet cutters can help accurately divide scored tablets, experts feel it is preferable not to cut pills to fractions below half [136]⁴. Using tablets that require cutting up, particularly unscored tablets, can result in the underdosing or overdosing of children, and this may lead to an increased risk of resistance or toxicity. Furthermore, doses cannot easily be adjusted as children grow, which may further contribute to underdosing or overdosing. As a result of competition from generic manufacturers and pressure from lobby groups, the prices of many antiretrovirals for adults have dropped significantly in recent years. However, while prices vary based on bulk procurement and negotiated rates for some developing countries, overall prices for the solid and liquid formulations of ARVs required to deliver standard first line therapy remain much higher for children. Promising generic products of FDCs for children such as Cipla and Emcure triple FDCs (d4T/3TC/NVP) are now being produced, although US, European or WHO regulatory approval has not yet been given as of October 2006. Regulatory authorities have improved guidelines on what submissions are required, but for originator and generic manufacturers there is still a lack of clarity on what dossier submissions will require. It is hoped that this situation will improve rapidly over the next 12 months.

Providing Simple Dosing Recommendations

Dosing in children is usually based on either body surface area or weight [66]. As these change with growth, the actual drug doses need to be adjusted to avoid the risk of under dosage. However, to facilitate service delivery and decentralization of the clinical care services programme management standardization of drug dosing is important. It is therefore recommended that national programmes develop and approve nationally relevant tables of simplified drug doses that can be administered at various levels in the health care system. While many of the ARV drugs have dosing indications based on body surface areas, this is not always easily calculated at all levels in the health care systems. It is therefore desirable to provide health care workers with dos-

ing recommendations based upon weight. Any such tables need to be developed and approved at the national levels, and may vary between localities in accordance with the availability of ARV drugs and formulations in the countries concerned. To assist this WHO has developed generic dosing tables and tools⁵ for countries to review and adapt in standardization and calculation of drug doses. National programmes guided by national expert panels need to review and adapt as appropriate. FDCs of standard first line therapies would greatly enhance the adoption and standardization of dosing across national programmes. The currently available adult fixed-dose combination formulations do not contain the appropriate doses of each of the component drugs suited for all ages. This is a specific concern for the NVP component of some adult-size fixed-dose formulations of zidovudine/lamivudine/nevirapine (AZT/3TC/NVP) and stavudine/lamivudine/nevirapine (d4T/3TC/NVP). Also the need to provide induction dosing of NVP means that for the first two weeks of therapy a single FDC containing all three drugs cannot be used. This should not however preclude the development of triple FDC combinations for children.

RESHAPING AWARENESS OF NEEDS: ARE RELIABLE DATA FOR PRODUCTION AND DEMAND FORECASTING OF FDC PAEDIATRIC ARVS ACTUALLY LACKING?

Background

Yet to-date only two solid-formulation paediatric FDCs, both d4T/3TC/NVP, are in late-stage development from generic pharmaceutical companies (Emcure and Cipla of India, and Government Pharmaceutical Organization GPO of Thailand) [23]. Their scarcity can be explained, in part, by the lack of demand generated in the developed world due to the success of PMTCT programmes in preventing paediatric HIV infection in these countries. In contrast, less than 10% of pregnant women living with HIV and AIDS in low and middle-income countries receive the required ARV prophylaxis to stem vertical transmission [85]. Thus from the point of view of the pharmaceutical industry, the market for paediatric ARVs – which exists primarily in poor countries with low PMTCT coverage -- may not present a sufficiently viable commercial venture to warrant concerted and sustained investment into production and research and development of ARVs for children. Thus not only are useful and effective formulations of paediatric ARVs not produced, those products that are available in the developing world are priced significantly higher – up to 10 times more expensive -- than their adult counterparts [119].

The apparent reluctance of the pharmaceutical industry to prioritize the development and production of paediatric FDCs may have a quantitative explanation as well. The market for paediatric ARVs is poorly characterized and quantified, as testing and monitoring of paediatric HIV cases is very poor in these countries. In addition, weight and surface-area based dosing for children make the paediatric ARV market extremely sensitive to temporal shifts (as children grow and gain weight), and raise questions about its economic sustainability from the perspective of an industry that

⁴<http://www.who.int/hiv/pub/guidelines/whopaediatric.pdf>.

⁵A web-based tool to assist in development of dosing tables was made available on the WHO website from mid 2006.

typically favors the development of products for "continued use". These factors have stalled the generation of reliable paediatric ARV forecasts, and thus have prevented the establishment of predictable demand and well-defined market projections for paediatric formulation ARVs. The economic disincentives caused by an inadequately defined market may explain the presence of relatively few pharmaceutical companies participating in paediatric ARV production and development of FDCs for children. In turn, the current non-competitive environment artificially preserves inflated prices for paediatric ARVs and has stifled innovation for new formulations.

The inability to adequately test and follow-up paediatric HIV has left an information gap that has, to-date, prevented accurate, reliable, and routine forecasts of paediatric ARV needs. Without estimates of the numbers of children in need of ART, and without basic consumption data for paediatric ARVs, both the allocation of funds for and thus the procurement of paediatric formulation ARVs has been slowed.

The data gap for paediatric ART is startling. There are currently no funding or implementing agencies, other than NGOs, that have made publicly available data on the number of children they currently have on treatment. Accordingly, there is a scarcity of figures on procurement and consumption of paediatric formulation ARVs. Only the Ministry of Health of Brazil [80]⁶ and the WHO Global Price Reporting Mechanism (GPRM) [99]⁷ have published paediatric ARV procurement data. Though the GPRM -- a very limited and self-selected dataset comprised of an amalgam of information from governments, funding organization, and procurement agents -- contains data from 44 countries reporting purchases of paediatric ARVs, this amounts only to 29,765 units purchased by the end of 2005.

This section examines whether the current paucity of data on paediatric HIV treatment and use of paediatric ARV formulations is, ultimately, too great a bottleneck to produce accurate forecasts for paediatric ARV needs. Specifically, can even the limited data available on paediatric treatment and, more generally, ART scale-up, be used in some method to estimate needs for fixed-dose combination ARVs for children, and thus, perhaps contribute to stimulating the more rapid pace of development and production of these sorely needed products.

Methods and Results

We propose that even without accurate testing and monitoring of pediatric HIV cases in the developing world, current global estimates and existing forecasts are, in the short term, sufficient to estimate future needs for paediatric treatment and to establish a market attractive enough to stimulate investment by the pharmaceutical industry. These figures, paired with the simplicity of treatment selection and dosing facilitated by fixed-dose combinations, can be used together to make crude forecasts of the needs for paediatric FDCs and also to estimate market value.

UNAIDS Forecasting

In November 2005, WHO, UNAIDS, and partner organizations convened a meeting to discuss the forecasting of ARV needs until 2010 [134]⁸ in line with the Group of Eight (G8) nations' resolution to ensure, "...as close as possible to universal access to antiretroviral therapy by the year 2010." [98]⁹. Presented here were forecasts based on current country-specific models used by UNAIDS and WHO to make estimates of ARV needs, and assumptions about the trends in HIV prevalence in 125 low and middle income nations [90, 91]⁸. These figures map a near-linear increase in ART coverage over the next five years, with an assumed ceiling of 60% coverage at 2010. ART scale-up in children was also forecasted, showing total need, coverage and the unmet need each year from 2006-2010.

The yearly estimates of numbers of children in need of ART presented by WHO and UNAIDS allow for quick and relatively simple forecasting of the paediatric ARV market for FDCs. Here we will only consider d4T/3TC/NVP and zidovudine/lamivudine/nevirapine (ZDV/3TC/NVP), in part because the limited country level data available has shown a high percentage of 3TC, d4T, AZT and NVP procurement relative to other paediatric ARVs [45]⁸. If we then assume that d4T/3TC/NVP will also be the most common 1st line regimen used in children in resource-limited settings, then we can segment the forecasted market amongst these two FDCs.

Table 2 presents scenarios of market size for the two selected paediatric FDCs, based on percentage of total children in need of treatment on each regimen. These percentages were determined, in part, by country-level data on adult first-line ART usage by combination which show that single-pill fixed dose combinations of d4T/3TC/NVP are the most commonly used, ranging from 45% [22]⁸ to, in the case of Malawi, 96% [118] under a standardized kit system. By the end of 2010, the total market size for paediatric treatment is estimated to be nearly 1,000,000 children. The percentage of children in need of ART on d4T/3TC/NVP could range from 697,000 to 896,000, depending on the scenario used. The UNAIDS forecasts could, additionally, be used for calculations of market value based on differential drug pricing schemes determined by country income level.

WHO Estimates for "3 by 5"

Alternatively, and even more simply, the latest WHO estimate of number of children in current need of treatment [85] 660,000, can be used to run additional scenarios that would calculate immediate treatment needs. This number is based, in part, on data from country level HIV programmes, bilateral and multilateral donor programmes, and NGOs who have reported to the WHO figures on paediatric treatment scale-up in support of the just-completed "3 by 5" target. Under the three scenarios presented in Table 2, current needs for an FDC of d4T/3TC/NVP would range from 462,000 to 594,000. Correspondingly, need for ZDV/3TC/NVP would range from 66,000 to 198,000 children.

⁶<http://www.aids.gov.br/monitoraids/>. [last access 2006, October].

⁷www.who.int/3by5/amds/price/hdd. [last access: October 2006].

⁸http://www.who.int/hiv/amds/geneva_nov7/en/index.html.

⁹www.fco.gov.uk/Files/kfile/PostG8_Gleneagles_Communique.0.pdf.

Discussion

The market forecasts presented above are by no means exhaustive nor inclusive of all considerations that would influence the evolution of paediatric treatment needs, and therefore warrant consideration in an accurate forecasting model of paediatric FDC ART demand. For instance, we did not account for rates of treatment-related toxicity in these two regimens (such as peripheral neuropathy, lipodystrophy, anemia, lactic acidosis etc.) resulting in substitutions between d4T and ZDV. Nor did we account NVP-related toxicities, such as acute hepatitis or Stevens-Johnson syndrome, that would require substitution with efavirenz (EFV) or a nucleoside reverse transcriptase inhibitor (NRTI), such as abacavir (ABC), as appropriate. We also did not consider TB/HIV co-infection in children, which would require a triple-NRTI first-line regimen of d4T + 3TC + ABC. For each of these factors, the data are very sparse from both the developed and developing worlds, due to the reasons outlined in previous sections.

In addition, we did not factor in expected increases in PMTCT coverage, which would reduce the number of new children per year who become HIV-infected. It is estimated that 700,000 children were newly infected with HIV during year 2005 alone in low and middle-income countries [113]¹⁰, under current PMTCT coverage rates of approximately 10%. This figure includes 13-42% of children infected by vertical transmission and from 5-20% due to breastfeeding [114]¹¹. Data on yearly increases in PMTCT coverage is poor, yet it is estimated that even with "universal access" to PMTCT services in pregnant women, defined as 80% coverage, 300,000 children will still be newly-infected per year [76]¹². Of these new infections, it is difficult to determine what percentage per year would be in current need of ART. In making such an approximation, one must also consider coverage with co-trimoxazole (CTX) prophylaxis in children, which has been shown to reduce mortality by 50% by delaying advancement of HIV disease. However, coverage with CTX prophylaxis is estimated to be only 1% in developing countries [24].

Our scenarios also did not account for advances in diagnostic testing in children. Available antibody tests used in adults cannot be used in children < 18 months old, due to circulating maternal antibodies present in their blood. Hence clinicians have been forced to wait until after 18 months, or more aggressively, make presumptive diagnoses of HIV infection in infants using clinical indicators such as failure to thrive and the appearance of opportunistic infections. Virological assays, such as DNA PCR, can be used to diagnose HIV in infants, but are currently priced prohibitively high (US\$10-125 per test and US\$ 7,000-40,000 for equipment) relative to antibody tests to be affordable for the majority of poor countries. In addition, PCR is also difficult to implement in settings without regular electricity and other infrastructure to preserve the integrity of the test reagents and equipment [23].

Dried blood spot (DBS) tests on filter paper have been proven reliable, and reduce the equipment, infrastructure, and human capacity needed at the facility to test infants < 18 months old for HIV [7]. Two versions of this test are currently under assessment by the WHO [7]. Improvements in diagnostic capacity in children < 18 months would not only result in a sharp increase in the number of known HIV-infected children, but also would increase the number of known children in need of ART.

A more sophisticated forecasting model using higher-quality data sources than were available to establish our assumptions, would by necessity have to balance any reductions in children in need of ART due to improved coverage of PMTCT and CTX prophylaxis, with an increase in the number of known HIV infections (and therefore an increase in ART needs) due to improved diagnosis in children. As diagnosis improves in infants, accurate forecasting would have to include needs for liquid, syrup, and powder formulations of FDCs. Finally, as coverage with ART in children increases resulting in prolonged survival, reliable forecasting of paediatric ART needs would also have to account for the transition of children from paediatric formula ARVs onto adult formulations as they grow in weight and surface area.

The data gaps described necessitate the improved monitoring of paediatric HIV cases in developing countries, and thus the continued bilateral and multilateral support for these initiatives. As paper-based and in some cases, electronic, patient monitoring systems [7] are implemented in treatment programmes in poor countries, the quality of clinical data on HIV-positive children on prophylaxis or treatment, will improve. In addition, accurate forecasting of paediatric ART will require improved logistics monitoring and supply chain systems for drugs and supplies necessary for the treatment of children. Improved data from paediatric treatment programmes at the facility, district/region, and national levels will provide a stronger evidence-base upon which to make procurement decisions for paediatric ARVs. From the perspective of donors and the pharmaceutical industry, strengthened monitoring systems will provide better global and regional data for the increased and sustainable financing of paediatric treatment, and for further investment into production and R&D of these products, particularly FDCs.

Despite the current limitations in available data, the crude models presented in this section provide a simple, yet compelling argument for the immediate increase of production and development of fixed-dose combination ARVs for children. From a short-term perspective, there is a market of approximately 660,000 children currently in need of treatment who would benefit from simplified and effective combination therapy in a single tablet. And this number will only increase as improved diagnosis and monitoring of children is scaled-up. Taking a long-term view, the estimated increase in needs, coupled with efforts to ensure sustainable financing for treatment *via* the Global Fund and PEPFAR, should quiet doubts that the financial resources do not exist to fund paediatric treatment in developing countries. Even under the very limited scenarios presented here, the market for paediatric FDCs is substantial, and is only poised to grow.

¹⁰http://www.who.int/hiv/epi-update2005_en.pdf.

¹¹http://www.unaids.org/epi/2005/doc/report_pdf.asp.

¹²www.globalaidsalliance.org/docs/UNICEF_IATT_report_June_2005.doc.

Table 2. Three Scenarios of Numbers of Children, in Low and Middle Income Countries, in Need of Treatment with Fixed-Dose ART Combinations d4T/3TC/NVP and ZDV/3TC/NVP (Based on UNAIDS Forecasting Data)

Country income classification	Yr	Children in Need of ART	90% d4T/3TC/NVP	10% ZDV/3TC/NVP	80% d4T/3TC/NVP	20% ZDV/3TC/NVP	70% d4T/3TC/NVP	30% ZDV/3TC/NVP
Low Income	2006	620,000	558,000	62,000	496,000	124,000	434,000	186,000
	2007	670,000	603,000	67,000	536,000	134,000	469,000	201,000
	2008	730,000	657,000	73,000	584,000	146,000	511,000	219,000
	2009	800,000	720,000	80,000	640,000	160,000	560,000	240,000
	2010	830,000	747,000	83,000	664,000	166,000	581,000	249,000
Lower middle income	2006	95,000	85,500	9,500	76,000	19,000	66,500	28,500
	2007	110,000	99,000	11,000	88,000	22,000	77,000	33,000
	2008	120,000	108,000	12,000	96,000	24,000	84,000	36,000
	2009	140,000	126,000	14,000	112,000	28,000	98,000	42,000
	2010	150,000	135,000	15,000	120,000	30,000	105,000	45,000
Upper middle income	2006	10,000	9,000	1,000	8,000	2,000	7,000	3,000
	2007	12,000	10,800	1,200	9,600	2,400	8,400	3,600
	2008	13,000	11,700	1,300	10,400	2,600	9,100	3,900
	2009	15,000	13,500	1,500	12,000	3,000	10,500	4,500
	2010	16,000	14,400	1,600	12,800	3,200	11,200	4,800
Global total	2006	725,000	652,500	72,500	580,000	145,000	507,500	217,500
	2007	792,000	712,800	79,200	633,600	158,400	554,400	237,600
	2008	863,000	776,700	86,300	690,400	172,600	604,100	258,900
	2009	955,000	859,500	95,500	764,000	191,000	668,500	286,500
	2010	996,000	896,400	99,600	796,800	199,200	697,200	298,800

Values represent numbers of children in need of each ART regimen.

THAI GPO'S WAY FORWARD TO SCALE UP ACCESS TO FDC PAEDIATRIC ARVS

Providing Paediatric Treatment

Children with HIV in Thailand face the same problems as HIV – infected children elsewhere. First, sometimes they are mistakenly perceived as having short life spans, thus treating HIV – positive children has not been regarded as a priority. Second, ART for adults [84]¹³ may not be appropriate for some children and paediatric formulas are lacking. Third, paediatric formulations are more expensive than adult ones. And where they are available, children may be reluctant to take them because they are unpalatable or cause unpleasant side effects. Finally, not enough effort is placed in keeping parents alive and giving them adequate support in providing care for their children. Lack of follow – up is also a major area of concern in the region because parents might not give their infants the correct dosage of ARVs, which could eventually lead to drug resistance.

Programmes in Thailand also need to tend to the psycho-social issues that infected children experience [10]. In addition, attitudes among health workers against infected children need to be addressed. Some health workers in Thailand

refuse to treat HIV – positive children because they are afraid of contracting the virus. Consequently, insufficient number of counsellors and health care providers are trained in meeting the special needs of children infected with HIV.

The move to place children at the center of the HIV/AIDS response will require strong partnerships with the ministries of public health and social welfare and planning, NGOs, communities and civil society to ensure access to treatment, protection, care and support.

Much more also need to be done to lower the cost of paediatric formulations. Regional medical institutions and pharmaceutical companies, particularly those making generic drugs play a crucial role in reducing the price tag. But it is also imperative that fairer trade rules are promoted, especially those regarding patents and intellectual property, which prop up prices [36].

The Thai Ministry of Public Health (TMOPH) launched an "Access to Care" program in 2000 to provide antiretroviral (ARV) drugs to HIV - infected patients as well as to improve the infrastructure of the medical services in hospitals participating in the program [21].

These ambitious plans are only possible because Thailand has the capacity of producing low-cost generic versions of antiretroviral drugs at about USD 300 per patient per year.

¹³<http://www.who.int/3by5/publications/documents/artmonitoring/en/>.

This compares to around USD 8,000 for similar drugs in Europe or North America [40].

Generic production of anti - retroviral drugs by the Government Pharmaceutical Organization (GPO) has brought down the price of the ARV drug, including the combination regimen. The prices have been lowering down to a level never happened before. The local generic production is a vital factor to enhance the national policy on the expansion of ART to cover a much more number of patients. It is also a prime factor to expand ART to be accessible to all in the later period [94]. The majority of the ARV drugs being provided are produced by the Thai Government Pharmaceutical Organization (GPO). GPO supplies pharmaceutical and medical products to support health service activities throughout the country as a state enterprise under the Thai Ministry of Public Health [100]¹⁴.

GPO has started manufacturing antiretroviral drugs since 1995 and begun to produce the paediatric ARV drugs since 2002. The first pediatric ARV that GPO manufactures is AZT (zidovudine) syrup (10 mg/ml) which can reduce the price of the drug from 30 USD to 3.75 USD. Until 2005, GPO manufactures 6 items of the paediatric ARV drugs such as ddl (didanosine) 30 and 60 mg powder, 3TC (lamivudine) syrup (10mg/ml), d4T (stavudine) for oral solution (1mg/ml and 5 mg/ml) and NVP (nevirapine) dry suspension (10 mg/ml). All the generic products can reduce the price of paediatric ARV drugs 10 - 30 times and make the access to HAART for children is possible.

In December 2001, GPO - VIR[®] was registered by the Thai Food and Drug Administration for treatment of HIV infection in adults. GPO - VIR[®], a fixed-dose combination (FDC) tablet of d4T, 3TC and NVP is available in two formulations, named based upon the dosage of stavudine. GPO-VIR[®] S30 (for adults, weight <60 kg) contains 30 mg of d4T, 150 mg of 3TC and 200 mg of NVP. GPO-VIR[®] S40 (for adults, weight ≥60 kg) contains 40 mg of d4T, 150 mg of 3TC and 200 mg of NVP [69]. The two formulations are listed as the first - line ARV drugs in the national treatment guidelines for HIV - infected adults as part of the *Access to Care* Program. The GPO - VIR[®] regimen has reduced ARV costs to the equivalent of \$30/person/month. The S30 formulation has been widely used in the HIV - infected pediatric population due in part to the lack of other affordable ARVs and the convenience and advantages of a FDC tablet. A similar paediatric formulation had not been available.

In 2002, the Thai Ministry of Public Health launched the National Access to Antiretroviral Program for People Living with HIV/AIDS (NAPHA) with the aim of providing treatment to all Thai patients with HIV infection. The program relies heavily on GPO-VIR[®] and the use of non - paediatric formulations is encouraged for children. A recent publication on the efficacy of HAART in HIV-infected children participating in the Program concluded that HAART (either NVP or efavirenz-EFV, together with 3TC and d4T) using generic drugs and/or adult formulations was safe, effective and feasible [86].

While there are few published studies of the use of GPO-VIR[®] S30 in children, a recent study of children aged 3 - 15 years was completed by investigators at Siriraj Hospital,

Chiang Mai University, and the University of California San Diego (Chokephaibulkit *et al.* personal communication, with permission). Thirty - five (35) HIV-infected children, who were stable on GPO-VIR[®] S-30 for more than 8 weeks, were enrolled. 15 of these children were treatment naïve; four were also receiving indinavir boosted with zidovudine. Children received an observed dose of the scored tablet ($\frac{1}{2}$, $\frac{3}{4}$, or full tablet, according to weight and the NVP dose of 120 - 200mg/M², every 12 hours). PK (pharmacokinetic) samples were drawn to assess NVP plasma concentrations. In the 34 evaluable subjects (18 female and 16 male) with a median treatment duration of 16.8 (2.7 - 27.5) months, the median CD4 count and percentage at baseline was 246 (10-1221) cells/mm³ and 20.3 (1.7-30.2)% at the time of the PK study. The median PK parameters and ranges were: AUC_(12h) of 78.4 (50-306.6) h*mcg/mL; C_{min} of 6.0 (2.6 - 24.4) mcg/mL; T_{1/2} of 25.5 (12.1-105.2) h; NVP clearance of 0.08 (0.02-0.16) L/kg/hr and V_d of 2.95 (2.7-3.2) L/kg (Chokephaibulkit *et al.* personal communication, with permission). The GPO-VIR[®] S30 FDC tablet can be administered to children over 3 years of age and will result in appropriate NVP exposure [101]. Most Thai children receiving this formulation tolerated it well and experienced sustained immunologic benefit.

GPO - VIR[®] Paediatric Tablet

In 2004, the GPO developed a FDC formulation of GPO-VIR S[®] containing d4T (7mg), 3TC (30mg) and NVP (50 mg) for pediatric use, and referred to as the " GPO - VIR S[®] Pediatric tablet". It is a chewable, citrus flavored, scored tablet that is taken twice a day (every 12 hours). The analysis results of the laboratory scale batch and the pilot batches indicated the required parameters had been met the specification. The accelerated stability results up to 6 months in market high density polyethylene bottle showed that the shelf life of the product is up to 24 months. The long term stability testing is underway. This formulation has currently been in the process to investigate PK study in HIV-infected children.

In 2005, the GPO developed a FDC formulation of GPO-VIR Z[®] containing AZT (50mg), 3TC (30mg) and NVP (50 mg) for pediatric use, and referred to as the " GPO - VIR Z[®] Paediatric tablet". It is a film coated, scored tablet that is taken twice a day (every 12 hours). The analysis results of the laboratory scale batches indicated the required parameters had been met the specification. The accelerated stability testing and long term stability testing are under investigation.

HOW TO IMPLEMENT STRATEGIES TO ENHANCE DEVELOPMENT, PRODUCTION, AFFORDABILITY AND APPROPRIATE SUPPLY SYSTEMS OF SUITABLE ARV DRUG PAEDIATRIC FORMULATIONS?

Current Barriers to Access to Paediatric Anti-Retroviral Formulations

The supply gap in accessing appropriate paediatric ARV formulations is not a unique phenomenon. Mismatches of needs, demand and supply of health services and commodities are well documented. Musgrove *et al.* did an analysis of health care needs, demands and supply on behalf of the World Bank in August 2005, creating scenarios of the ways health systems can go wrong [77].

¹⁴<http://www.gpo.or.th>.

In an ideal health system, it is assumed every true need for medical care would generate a demand for an appropriate service, and the marketplace supplying services and commodities would meet every demand. Unfortunately, often need, demand and supply do not coincide, leading to three kinds of 'mismatches':

Mismatch of *needs* and *demands*, Mismatch of *needs* and *supply* (of services and hence, also to commodities), and Mismatch of *supply* and *demand* (Table 3).

A market is in essence an information system [137]¹⁵. In an ideal marketplace, the right products at the lowest possible cost should be available at all times because the market is able to transmit all the information about costs and benefits between producers and consumers. If any aspect of this information flow is imperfect, the market will fail. It is therefore inevitable that lack of information affects all three of the failures defined above, but in different ways [77]. This paper by no means attempts to portray an economic analysis of current market for paediatric ARV formulations. However, ignoring the basic economic principals driving equitable access to paediatric ARV formulations could result in failure to interest the market, overinvestment due to inefficiencies, gaps in supply and oversupply.

Strategies to Enhance Development, Production, Affordability and Appropriate Supply Systems of Suitable ARV Drug Paediatric Formulations

Given the immaturity of the market for paediatric ARV formulations, it is necessary to consider strategies to assess and address all contributing factors leading to mismatches between need, demand and supply (Table 3).

CEF/UNAIDS publication: A Call to Action: Children, the missing face of AIDS [117]¹⁶. Global targets have been set, and the goal to achieve 80% coverage of needs by the 2010 has been endorsed by most political leaders in highly affected countries. However, global targets alone will not create the necessary demand to ensure coverage of treatment for 80% of children in need. Reaching the more than 860,000 children under 15 years of age living with HIV AIDS in Africa with appropriate ARV formulations will require a country-by-country forecast of Need, balanced with Demand at the local level.

Today the main contributing factors to the mismatch between need and demand for paediatric ARVs are those hampering the early identification of children in need of treatment. In addition to lack of planning and stigma related barriers, factors such as lack of laboratory infrastructure and capacities, complicated testing procedures and cost barriers further compromise the upscale of programmes that can drive the demand for paediatric ARV formulations. The Unite for Children, Unite for AIDS Campaign are advocating for a number of major actions to be supported by implementers of programmes, all of them with the potential advantage of reducing the imbalance between need and demand:

- Cotrimoxazole prophylaxis programmes from 6 weeks of age until HIV infection is ruled will inevitably increase awareness of HIV status and available options for care.
- A public health approach to paediatric HIV treatment and care, and linkages with existing child survival programmes will not only increase opportunities to enter into care, it will simplify training and reduce

Table 3. Examples of the Factors Potentially Affecting the Need, Demand and Supply of Paediatric ARV Formulations

Mismatch between NEED and DEMAND	Mismatch between NEED and SUPPLY	Mismatch between DEMAND and SUPPLY
Lack of information (Ignorance): The HIV status of infants may not be known; even if it is known (+), caregivers may not know treatment is available	Lack of information (knowledge of prescribers): Paediatric ARVs has to be prescribed by a provider with some training. A lack of capacity may widen the gap between need and supply.	Lack of information (on real needs): In normal competitive markets, the drive is to fulfil the demand. Where need and demand is distorted, inequality in access will ensue.
Costs (to patients). Even if ARVs are given free, associated costs may be catastrophic. (e.g. user fees, testing costs, hidden costs such as transport over long distances, in the case of referral to specialist centres).	Costs (to systems): The decisions to provide services and therefore access to treatments may not lie with beneficiaries, but with health care managers who may decide not to provide 'costly' services	Barriers to competition: Patent restrictions limiting use of generic products. Delays in regulatory approval, especially with Fixed Dose combinations for paediatrics.
Externalities: Some economists distinguish between 'selfish' and 'caring' externalities. Selfish externalities can affect demand, for example, in willingness to pay for a child's care. Some people benefit from knowing that others are receiving care, i.e., 'caring externalities'. This concept may explain why some people are prepared to pay additional taxes.	Market Incentives (Profit): Industry, and the market driving the supply of these formulations, may be profit driven. Hence, even in situations of need, the market may not respond in supply.	Non-market incentives (government provided services): Public programmes typically try to match need with supply. However, where patients have to demand services to receive it, ignoring demand and matching supply needs can lead to excess supplies (waste) or supply shortages.

Adapted from Musgrove P, 1995 [77]: Causes of mismatch among need, demand and supply of health services.

Balancing Need and Demand for Paediatric ARV Formulations

The *need* to address the gaps in prevention of HIV infection in children, care and support for children living with HIV AIDS has been addressed unmistakably in the UNI-

costs as resources are shared among existing programmes.

- Keeping parents alive have the potential of sustaining care in a family driven model, fostering continuity of care in various ways.

¹⁵<http://en.wikipedia.org/wiki/Market>.

¹⁶http://www.unicef.org/uniteforchildren/files/U77HIV_letter.pdf.

The costs to patient accessing paediatric ARV formulations remain a barrier regardless of price decreases observed over time. Considering the fact that HIV AIDS is a chronic condition, appropriate locally defined strategies is needed, not only to cover the drug costs, but accessing services may require user fees and travelling long distances may also introduce additional costs. Financial protection to users of paediatric HIV care and treatment programmes is essential, not only considering the inclusion of the very poor in health care financing strategies, but also recognising that universal access requires all households to be protected against catastrophic health expenditures [130]¹⁷.

Balancing Need and the Supply of Paediatric ARV Formulations

It is essential to articulate the needs and interventions driving the supply of paediatric ARV formulations in such a manner that they are recognised as effective and affordable and as an appropriate response to society's demand for the protection of the health of all citizens. Sustaining the supply of paediatric ARV formulations for as long as the need persist will require recognition of all the factors affecting chronic disease management programmes. Strengthening health systems are a fundamental part of these interventions [131]¹⁸. Major challenges facing these programmes are, among other:

Channelling funds effectively, the challenge being the ability to capture different sources of funding, to scale up both access and financial protection in a stable and predictable manner.

Meeting the need for providing universal access to paediatric ARV formulations will require a well defined backbone of *decentralised service delivery and supply system*.

The challenges in *creating a human resource base for paediatric AIDS care*.

Ensuring continuity of care, handing over the responsibilities of care from neonatal care, to child health care and finally transitioning to access care through adult and adolescent services.

Many of these challenges are incorporated in other health care improvement and child survival programmes, and an integrated approach to addressing them is essential [129]¹⁹.

Given the statistics quoted on children enrolled in treatment, it is clear that there are substantial mismatches between need and supply of ARV formulations. Initiating supply has the potential to contribute to correcting them. Formulations to treat children of all ages are available, and children should be enrolled into treatment programmes as a matter of urgency. Fixed dose combination products for children and other user-friendly formulations are in the production pipeline. The challenge is to get them into the supply systems as soon as possible. By building on valuable lessons learnt, undesirable market outcomes can be avoided. Economists often evaluate market response against the theories of market

failure [108]²⁰, non-market failure and/or government failure, among other [33]. Since market failures occur fairly frequently, various organisations and institutions provide guidance to public sector institutions on creating markets [81]²¹. These guidelines include not only activities, but also ideal behaviours to adopt in order to stimulate markets to respond to requirements. Four key recommendations that can be applied to the marketplace supporting access to paediatric ARV formulations include:

Careful planning before approaching the marketplace, to understand the environment, to analyse the position of suppliers and identify factors that can inhibit responses.

Early engagement with supply chains, regardless of whether it is a local or a global supply chain, to shape the requirements and to ensure transparency in business processes.

Defining requirements in such a manner that suppliers can come up with novel approaches to reach desired outcomes, combined with a willingness to be flexible when it comes to the commercial/contracting options, e.g. contracting with multiple suppliers, geographical splits.

Ensuring commitment and effective organisational management. Commitment at the highest level to support the process from start to end is absolutely essential. Transparent, rigorous procurement and supply management procedures and appropriate skills must be available in the procurement and supplies management team.

The suppliers' perspective in the case of a paediatric ARV market needs to be appreciated. Suppliers receive many calls on their resources, and every business opportunity presents not only benefits, but also potential costs and risks. Suppliers are profit driven, and review prospects at each stage of the process. They may decide at any point of time to withdraw if the outcome is perceived as negative. Managing the process of market creation and initiating supply in a transparent and efficient manner is therefore of critical importance.

Balancing Demand and the Supply of Paediatric ARV Formulations

In addition to the programmatic factors distorting need and demand described above, a number of product specific factors may affect demand and supply. Not all the WHO recommended ARVs are produced in formulations that are palatable, feasible and/or acceptable to use in resource poor settings. Calculations of dosages of individual formulations are complicated and large volumes of liquids needed for treatment, short shelf-lives of products and the need for cold storage complicate supply planning and management.

Special procedures when dispensing medicines to patients are often required, not only to control the supply, but

¹⁷ http://www.who.int/health_financing/pb_2.pdf.

¹⁸ http://www.who.int/health_financing/issues/mechanisms/en/.

¹⁹ <http://www.who.int/mdg/publications/02MDGChapter2.pdf>.

²⁰ http://www.tutor2u.net/economics/content/topics/marketfail/market_failure.htm.

²¹ http://www.ogc.gov.uk/sdtoolkit/deliveryteam/procurement/market_creation_guide.pdf.

to guide instructions to caregivers [135]²². Fixed-dose combination products with simplified dosage instructions such as a once or twice a day regimen, as is used in adult care, is essential to sustain a public health approach to the treatment of children and young infants.

Fixed Dose combination products will not only simplify and facilitate treatment, the cost of treatment can be reduced to up to half of the current generic treatment cost per month. To benefit from these developments, high burden countries need to assess barriers to entry into the local market. Patents and licensing agreements apply in most of the high burden countries, and governments will need to make use of flexibilities in trade legislation to access these products. Delays in regulatory approval should be anticipated. Existing delays in getting marketing authorisation of up to two years are reported in some of the most affected countries. For these newer formulations, review of dossiers may be delayed further in countries where there is lack of capacity in the regulatory authorities. Submitting dossiers to the WHO prequalification scheme as soon as possible is recommended, since this mechanism can allow fast-tracked regulatory approval. For example, regulatory authorities may adopt the decisions made during the prequalification process and not duplicate reviews, or delays due to incomplete dossier preparation may be avoided.

Building an Efficient Global Supply Chain for Paediatric ARV Formulations

Managing demand, aligning activities of buyers, suppliers and end-users, optimising the operations of supply chains to reduce inventories and operational costs and quality assurance are aspects that can facilitate the global supply of paediatric ARV formulations and provide the transparencies that are needed to interest the industries involved. However, sourcing in multiple countries comes with complexities regardless of the type of commodity in question [63]²³. Challenges and barriers to building and accessing global supply chains include, among other, uncertain political stability, lack of infrastructure in some countries, lack of critical market mass in particular countries, high transaction costs due to some environments in which supply will be initiated, and slower adoption of e-business in least developed countries. Nevertheless, these challenges can be overcome by defining strategies and using existing tactics that are supportive of efficient supply chains.

Of highest importance is the need to strengthen information sharing, to monitor the flow of funding and products and provide accurate demand forecasts to industries. Good information management also has the potential to minimise investment in inventories, especially through electronic linkages to communicate and release supply requests and reports. Creating monopsonies, these are markets similar to monopolies, except that it is large buyers that dominate the market and drive prices down and not suppliers have potential to facilitate rapid market creation for paediatric ARVs. Centralising functions and pooling resources will assist with overcoming the initial global supply barriers efficiently. If managed appropriately, the availability of aggregated infor-

mation and coordinated demand and supply management could be particularly useful in the early phases of scale up when demands are erratic. With effective demand optimisation, manufacturers can plan production and therefore reduce transactional costs, and inventories can be managed. However, the long term effects of such strategies on a free market system are unclear. Where there is a potential for a viable market to develop, transitioning to allow free market forces to operate should be built into the design of the any centralised intervention.

COMBINATION INCENTIVES TO GENERIC COMPANIES TO BOOST MANUFACTURING OF AFFORDABLE FDC PAEDIATRIC ARVS AGAINST MARKET UNATTRACTIVENESS AND ENFORCED INTELLECTUAL PROPERTY RIGHTS

Trading and Marketing Constraints

The market for paediatric ARVs in the United States (U.S.) and Europe is very small: less than 1,000 new cases during year 2005 alone compared with an estimated 540,000 (420,000-670,000) newly infected children in the developing world (mainly Africa) [5, 29, 112, 132]²⁴. Consequently, there is no incentive for brand-name western corporations to develop new ARV formulations for children because they aren't considered a lucrative market. Difficulties are compounded by the fact that treating children is associated with much higher costs than adults [31, 115]²⁵.

In such a context, generic producers in the developing world, despite their willingness to meet the needs [56], have to cope at least with demanding WHO pre-qualification requirements that include shelf-life, dissolution and bio-equivalence studies as well as PK studies in children.

Challenges are complicated by regulatory obstacles bound up with enforcement of TRIPS (Trade-Related Aspects of Intellectual Property) rules inside the World Trade Organisation (WTO) [142]²⁶ (Table 4). Definitely, patent rules, along with exacerbated data-exclusivity rules (Table 5), do hamper the development of generic fixed-dose ARV combinations, especially when patents on the different compounds are held by different companies. Overall, exacerbated data-exclusivity not only impacts generic versions of individual ARVs, but FDCs that contain a drug with exclusive status [28]²⁷. Insightfully, this is a worrisome reality based on second generation medicines, as well as any new drugs are crucial to HIV treatment programs once first line ARVs fail [54, 64, 65, 68]. Presently, data-exclusivity bars application for U.S. approval for generic versions of atazanavir, emtricitabine, tenofovir, as well as of Gilead's Truvada (emtricitabine+tenofovir) and GlaxoSmithKline's Epzicom (lamivudine+abacavir) [58]²⁸.

Conversely, generic manufacturers, despite the hurdles they are facing, seem not to be basically lacking a business case to justify uncertainties whether starting with production of suitable FDC paediatric ARVs. It would be expected, indeed, that drug companies, while applying to HIV-infected

²²<http://www.who.int/3by5/en/finalreport4Apr.pdf>.

²³<http://www.ism.ws/files/Pubs/Proceedings/FEKauffman.pdf>.

²⁴www.unaids.org/epi/2005/doc/EPIupdate2005_pdf_en/epi-update2005_en.pdf.

²⁵<http://www.accessmed-msf.org/documents/sources.pdf>.

²⁶http://www.wto.org/English/tratop_e/trips_e/intel2_e.htm.

²⁷www.accessmed-msf.org.

²⁸www.healthgap.org/press_releases/05/1105_PWATCH_HGAP_BP_PROC.pdf.

children needs, will expand their market wherever a suitable family-hood is caring for their kids [38]. In these widely represented environments, indeed, also adult family members will possibly enjoy ARV treatment opportunities together with their children [20, 32].

Unfortunately, these considerations can only assuage the worries based on the numerous hurdles to the development and marketing of appropriate FDC ARVs for children. Hurdles bind up with the fact that paediatric formulations are a niche product in income-constrained countries where accurate demand forecasting is currently difficult to be achieved [51].

Shaping the Future: Key Role for India and China's Enforced TRIPS Management

As WTO member states, almost all countries are requested to follow the 1994 WTO Agreement on TRIPS (Table 4) [142]²⁶. China implemented patent regulation in 2002, while TRIPS compliance took effect in India on 1st January 2005. Overall, these two countries account for half the world's poorest population. Their big industrial plants supply most of their domestic needs while exporting high volumes of drugs to the under-served markets [138]²⁹. India and China are, moreover, the major suppliers of active pharmaceutical ingredients (APIs) for ARV drugs to both developed and developing countries [55]³⁰.

The outcomes of India and China management with enforced TRIPS rules are of utmost interest as they are expected to ultimately affect the availability, affordability and accessibility of ARV drugs inside most resource-limited country markets on a planetary scale [31].

India's Hindering Legislation: What Loopholes?

Although much of the developing world currently depends on Indian generic ARVs, recently revised Indian patent law (as in its 5th April 2005 amendment)³¹ has, unfortunately, posed a threat to keeping on affordable ARV treatment access.

Based on the new Bill, indeed, 1995-2005 "mailbox" medicines and newer drugs whose generic versions have not yet produced by Indian firms can only be sold as branded originals unless compulsory licenses (CLs) (Table 4) or direct agreements between the patent holders and Indian generic manufacturers have been undertaken. Conversely, Indian companies now manufacturing generic versions of medicines for which patent applications were submitted prior to 1st January 2005 are allowed to keep on with manufacturing and marketing, provided that they have made a "significant" investment and pay a "reasonable" royalty to the patent owner³¹. But, what do the adjectives "significant" and "reasonable" exactly mean? It is clear that, having not fixed parameters for unequivocal interpretation, the Bill will boost litigation problems with the patent holders. Moreover, it is definitely clear that, without incentives by Indian government, the prices of "generics" produced under such a royalty imposition will increase sharply making these drugs unaffordable by the poor [31, 70].

In such a context, CLs are unlikely to be issued by Indian government because of threats to keeping on with partnerships with research-based enterprises along with risks of blackmail by wealthy country governments and multinational corporations as all of these would be detracted from profits.

Conversely, TRIPS-bound voluntary licenses (VLs) (Table 4), if softened in their royalty imposition through incentives to firms, could actually help Indian manufacturers overcome the hurdles by enforced TRIPS while keeping drug prices low (see later).

China's Opening into the Future?

China could possibly become, in the next future, the ARV factory for the developing world because of both its cheapest APIs for ARVs and its expanding industrial scale-up [145]³². Chinese producers are already making first-line ARV formulations, as well as the raw materials for a wide array of first and second-line ARV drugs [106]³³.

Whether or not China will be able to routinely produce second-line ARV formulations, will depend on whether China is willing to exploit TRIPS flexibilities or, that is the same, will depend on concessions made when China joined WTO. Actually, China is under pressure nowadays for its weak pursuance of TRIPS rules [34]³⁴. Nonetheless, Chinese government, apart from reluctance to streamline commercially risky CLs, should expectedly be attracted by TRIPS-bound VL flexibilities (Table 4), just for a number of reasons:

- the need for technological catch-up while aiming to compete with the multinational giants.
- the need for trustworthy relations with research-based companies while looking for the standard above.
- the need, based on huge national epidemic, to enhance domestic production of suitable ARVs including FDCs and paediatric formulations, all of which are not produced in China yet [1, 31]³⁵.
- the need to achieve sustainable self-sufficiency in pharmaceutical manufacturing, so breaking away from dependence on fickleness and price fluctuations by foreign corporations.
- the awareness that reduced prices as per cutting by western drug producers would hardly be as affordable as those of "generics" produced domestically under VL agreements equitably softened in their charge.

Expanded production and marketing levels currently achieved by Chinese company Desano may be taken as an attuned model to overall considerations above (Table 6).

Brazil, Thailand and South-Africa Perspectives

Brazil, Thailand and South-Africa, though unreliable to equal India and China's predictability in securing poor countries second-line ARVs for paediatric and adult needs, present, however, with some chance to do so. This mainly depends on whether national companies will be capable of

²⁹www.who.int/medicines/organization/par/World_Medicines_Situation.pdf.

³⁰http://www.dfidhealthrc.org/shared/know_the/publications.html#access.

³¹www.patentoffice.nic.in/ipr/patent/patent_2005.pdf

³²www.sciencemag.org.

³³<http://web.amfar.org/treatment/news/TADoc7.pdf>.

³⁴http://www.dfidhealthrc.org/shared/know_the/publications.html#access.

³⁵www.chinaaids.cn.

transacting profitable negotiations with multinational counterparts [61]³⁶. To this aim, VL flexibilities, together with WHO brokerage, should always be part in transactions [8]³⁷.

Combination Incentives Inside Shared Strategy Directions

Presently, generic FDCs of stavudine/lamivudine/nevirapine for paediatric use are being produced by very few manufacturers including Thai GPO (Government Pharmaceutical Organization), Indian Cipla and Indian Emcure [95, 107, 39]^{38,39,40}. Combination incentives inside shared strategy directions are urged to implement these early results.

Making Directions Uniform

Under requirements above, WHO and UNICEF are sharing commitment to:

- push for pre-qualification of second-line generic ARVs for children as well as develop optimised dosing tables suitable to poor countries.
- dialogue with firms, as well as meet them and donors to clarify the needs and steps to be undertaken.
- identify generic (and, possibly, originator) firms who might be willing to deliver FDC paediatric ARVs and explore with them how to expedite such products for WHO prequalification or national registration.

Coherently, WHO and UNICEF, aiming to boost willingness of generic producers, have already encouraged major donors (including World Bank-WB, Global Fund to Fight AIDS, TB and Malaria-GFATM, as well as Clinton, Gates and Elisabeth Glaser foundations) to express their interest as purchasers.

Again, full cooperation is urged between the Office of PEPFAR (President's Emergency Plan for AIDS Relief) Global AIDS Coordinator and the WHO Pre-qualification Project to speed approval and prequalification of generic ARVs, including FDCs either for children or adults [43]⁴¹. This means that U.S. Congress should mandate the Office to waive coercive data-exclusivity rules which currently prevent Food and Drug Administration (FDA) approval of generic ARVs. The Office should also be allowed to waive restrictions forbidding purchase of WHO pre-qualified generic ARVs whenever supply shortages from brand-name PEPFAR suppliers may generate a freeze-effect on treatments. Moreover, the Office should inform all relevant embassies and PEPFAR contractees when FDA has granted tentative approval to generic ARVs. Furthermore, the Office should authorize with no delay procurement of FDA approved generic ARVs. Requirements above should ground on efforts to concurrently secure several manufacturers, as well as affordability and compatibility with national treatment protocols [58]⁴².

Actually, March 2nd, 2006 U.S.-India signed "civil nuclear power" agreement [120]⁴³ is expected to substantially fill the gaps just detailed. Predictably, indeed, it will play as a boost to expand PEPFAR use of Indian generic ARVs.

Boost to expand ARV therapy access by children is also expected by the new PEPFAR-released public-private partnership for paediatric AIDS treatment encompassing innovator and generic pharmaceutical companies along with UNICEF and UNAIDS [109]⁴⁴.

Modelling Combined Incentive Pool

Generic companies currently present as the most fitting target for incentives to tackle ARV treatment needs of children in the developing world. In such a light, support to generic companies is urged to stimulate competition with research-based corporations as far as the penetration of profitable markets is concerned. Actually, based on health sector and social security progresses steadily registered in sub-Saharan African countries [50, 89]^{45,46}, there is expectation that profitable HIV treatment markets for children will open there shortly. In such a perspective, western multinationals will necessarily try to enter these markets through negotiating partnerships and agreements aiming to regain wasted time and reduce the gap with high-level technology, market penetration and attraction power already achieved by their generic counterparts. These processes, by enhancing competition among all involved parties, will ultimately slash the drug prices.

According to insights above, WHO and UNICEF should explore with partners combined incentives for generic manufacturers to develop both affordable and appropriate FDC paediatric ARVs. These incentives should encompass public, private and/or intergovernmental subsidies using public-private partnerships, fiscal drug softening, as well as funding and streamlining of patent rules. Funding should be provided by governments and major international donors, based on generic companies do accept WHO pre-qualification check. Funding could even arise through giving African governments support to meet their commitment, as in Abuja Declaration, to devote 15% of national GDP (Gross Domestic Product) to health sector spending [2]⁴⁷. This would quite be attainable if debt cancellation to poor countries by G8 Heads of State and Finance Ministers will fully be met [50, 87]⁴⁸.

Definitely, overall insights above highlight the reasons for building, according to already working examples [31], domestic plants for generic ARVs in Sub-Saharan Africa as well. Domestic plants would play as a prerequisite for negotiating, through WHO brokerage, profitable VL agreements encompassing equitably expanded ARV drug access by infant and adult populations. Really, a credible industrial potential would act, indeed, as a boost for drawing branded drug producers into technology transfer agreements the terms of which would let all contractors enjoy substantial

³⁶www.aidsmap.com/en/news/24B33FA6-89CB-42BA-880F-18D774FF85D6.as.

³⁷www.sharedata.co.za/sens.asp?id=82577.

³⁸www.aegis.com/news/re/2004/RE040750.html.

³⁹www.cipladoc.com/html/newintrocippla.htm.

⁴⁰www.thehindubusinessline.com/2005/03/12/stories/2005031202210200.htm.

⁴¹www.avert.org/aidsnews.htm.

⁴²www.healthgap.org/press_releases/05/1105_PWATCH_HGAP_BP_PRO_C.pdf.

⁴³http://news.yahoo.com/s/afp/20060302/ts_usindiabushnuclearpoliticsdeal.

⁴⁴www.usa.no/usa/policy/article.html?print=1&id=6654&PHPSESSID=bd9b022...

⁴⁵www.dfid.gov.uk/g8/milestones.asp.

⁴⁶http://www.economist.com/world/africa/PrinterFriendly.cfm?Story_ID=2685783&ppv=1.

⁴⁷www.uneca.org/adf2000/Abuja%20Declaration.htm.

⁴⁸www.africa-union.org/root/au/conferences/past/2006/may/summit/doc/en/SP_PRC_ATM21_concept_paper.pdf.

advantages. Under such a perspective, the Chinese APIs could definitely serve as an affordable source for allowing domestic sub-Saharan plants to take off. This sounds consistent with Chinese increasing interests in Africa as documented by China's multi-pronged bilateral agreements currently being signed with many African countries and encompassing -though not limited to- trade, energy supply, investments, as well as infrastructure and health cooperation (China's African Policy, January 2006)⁴⁹.

Incentive-Bound VLs as a Key Option

Based on whole thoughts here, VLs (Table 4) are expected to play as a working strategy notwithstanding they provide for royalty rates imposition on generic firms: these licenses, indeed, only imply straightforward agreements between firms; they do not require changes in national legislation, while including non-exclusivity, openings towards technology transfer, access to owner's data for branded drugs as well as permission for export (Table 4).

In such a perspective, the growing potential of Indian and Chinese plants (enhanced by November 2006 China-India signed key trade agreement, as part of wider South-South and North-South partnerships) [144]⁵⁰ could act at once as a catalyst for VL agreements grounded on profitable conditions for the developing country firms as a whole.

Really, VLs appear as a key choice nowadays because research-based corporations are secured economic profits, while advantages to developing country firms are enjoyable as well: these include domestic market expansion as well as technology transfer and R&D partnerships which play as prerequisites for enhanced competition capability in the western markets.

This model, again, as not affecting low-cost API provision to developing country-based (Brazil, Singapore, Chile, Thailand, South-Africa...) generic firms depending on major APIs producers, would help allow these firms to keep on with domestic ARV drug production. Such a policy would also be crucial in helping least-developed countries with no manufacturing capability still import affordable generic ARVs without engaging in hardly feasible CL-bound changes in national law (Table 4).

Equally important, high-grade predictability of HIV resistance mutations in the developing world does allow VLs to be assigned another spin-off which links in with urgency for second-line and newer ARV drugs [31].

Clearly, owing to royalty imposition, VL frames should provide combination incentives to generic firms. These incentives, aimed to keep prices as lowest as possible, are first expected by country governments and international players including GFATM, WB, WHO and the Joint United Nations Programme on HIV/AIDS (UNAIDS). Based on complementarity with all of these institutions, the recently launched UNITAID-International Drug Purchase Facility [13]⁵¹ is expected, if fully and stably implemented in its dedicated revenues, to substantially help combination incentive strategy succeed. Basically, these incentives should comprise:

- ***Warranties of market expansion and safety as per "generics" exclusive bulk purchasing by international donors, based on acceptance by firms of WHO prequalification surveillance***

These agreements would meet the need for economies of scale to attract interest from generic manufacturers. As a reply to extremely urgent needs, they would ethically be warranted and would result in reduced drug prices thanks to the certainty of a growing market. Transparency and accuracy enjoyed through WHO prequalification check would make this model quite trustworthy.

- ***Warranties of fiscal relief by country governments***

Where from could governments draw the equivalent for such a tax allowance? Apart from enhanced disbursement by international donors and engagement in domestic expenditure priority reallocations, the debt relief savings from debt cancellation to poor countries would really free large sums of money that should partly be used to help meet HIV treatment targets. WHO and UNAIDS, following acknowledgement of country pledges to channel debt relief savings towards tax allowances, should engage in promoting approval of debt cancellation and closely checking for pursuance of the pledges.

- ***Warranties of WHO brokerage in VL agreement negotiations with research-based corporations***

As channelled towards knowledge and technology transfers along with R&D partnership opportunities, these regulated agreements mean as incentive for technological catch-up and easier access to profitable wealthy markets by developing country generic firms while ensuring equitable drug access by poor people as well.

Closing Remarks

VL use must be enhanced in transactions between western multinationals and generic companies as far as second-line ARV drugs, including newer FDCs for children, are concerned. VL use, indeed, would allow generic manufacturers to overcome enforced patent protection rules while being not barred by coercive data-exclusivity rules which do hurdle, instead, CL use (Table 5). WHO's brokerage should routinely be sought in these transactions. Definitely, WHO's role as broker and promoter in North-South VL-bound partnerships is expected to ensure equitable negotiations. Again, WHO's teaching role in good manufacturing practices (GMPs) should keenly be sought and be directed foremost towards highest epidemic burden countries to support generic companies in performing licensing/registration for paediatric products, as well as to fast-track national licensing/regulation and international pre-qualification requirements.

Based on their potential including suitability for meeting requirements and needs by all parties, VLs do appear as the preferred formula nowadays with advantages over CLs, differential pricing or donations (Table 7) [30, 31]⁵².

⁴⁹<http://www.fmprc.gov.cn/eng/zxxx/t230615.htm>.

⁵⁰<http://yaleglobal.yale.edu/article.print?id=4240>.

⁵¹www.franceonu.org/article.php3?id_article=1243.

⁵² <http://www.dfid.gov.uk/pubs/files/pharm-framework.pdf>.

Table 4. Trips Regulatory Terms and Dates for Patent Status of Drugs in Low-Income Countries

Patent	A twenty- year warranty securing inventor exclusive rights on the overall drug production and marketing aspects. When countries signed up to World Trade Organisation (WTO) they accepted to protect the patent rights of corporations selling drugs within their boundaries.
TRIPS (Trade-Related Aspects of Intellectual Property Rights) 1994	WTO Agreement to the safeguard of Intellectual Property Rights (IPRs) around the world. It protects companies by stopping anyone from copying their products for twenty years at least.
Drugs invented before 1995	No need for patent protection by a WTO member State if drugs were not patented before 1995, i.e. before TRIPS came into force.
1995-2005 “mailbox” drugs	It refers to 1995- 2005 invented drugs (including second-line ARVs) for which WTO members which did not recognise drug patents before 1995 were offered diversified time limits to become TRIPS-compliant. Transitional countries have to hold patent applications on these drugs in a so-called mailbox and secure patent applicants exclusive marketing rights (EMRs) for five years once drug was in the mailbox and registration was made by the national drug regulatory authority.
Post-2005 drugs	All WTO members, with exception of least-developed countries (LDCs), are requested TRIPS compliance.
Dates for LDCs	LDCs have to become TRIPS-compliant by 2006 but, if national legislation has been consistently amended, they are exempted from accepting patent protections and TRIPS enforcement until 2016. Aside from this flexibility, even LDCs have to issue compulsory licenses (see below) for importing copies of drugs already patented in pre-TRIPS domestic law.
Doha Declaration November 14, 2001	It stated that each WTO member has the right to use TRIPS-encompassed flexibilities (which include compulsory and voluntary licenses) to secure universal access to drugs in the face of a public health need.
Compulsory license (CL)	It is when a poor country government allows to manufacture domestically or to import copies of patented drugs at prices much cheaper than those imposed by the patent holder and without his consent. Both importing and exporting countries need to have enabling legislation in place (a corresponding CL for export has to be issued by the exporting country). Prior negotiation with the patent owner for voluntary license first is required unless for situations including extreme health crisis and not-for-profit government use. Payment of a royalty to the patent owner is encompassed by CL rules.
Voluntary license (VL)	Agreement negotiated with the patent’s owner for manufacturing and marketing. Notwithstanding royalty rates imposition on generic firms, these licenses only imply straightforward agreements between companies; they do not require changes in national legislation, while including non-exclusivity, openings towards technology transfer, access to owner’s data for branded drugs as well as permission for export.
Decision August 30, 2003⁵⁴	It allows non-manufacturing countries to issue a CL to import a generic version of a particular medicine based on a CL for export issued by the exporting country government. Declaration by the non-manufacturing country of insufficiency in manufacturing the specific drug is required. WTO change approved on 6 December 2005 made the Decision permanent [75] ⁵⁵ . So far, Norway, Canada, India, the EU, Netherlands, Korea and China have altered their laws to meet conditions for export.
Parallel importation	Importing of fairly priced patented drugs for which the rights of the patent owner have been exhausted by the first sale.
Bolar exception	Permission to a generic firm for copying and registering a patented medicine before patent expiry. It could exceptionally be applied only if the normal rights of patent holder are pledged.
Data exclusivity	Data protection against unfair commercial use only (but five and eight year protection have been respectively requested by U.S. and EU).

In economic terms, combination strategies as discussed here mean as incentive for generic corporations to enter under-served markets with extant copies of ARV products for children while concurrently investing in new FDCs for them. These perspectives bind up with long-term trade and drug policy directions of China and India according to frontier crossing implications of their TRIPS management and penetration strategies of both the wealthy and under-served markets worldwide.

Insights in this section also mean that the trade and profit rules cannot basically be given up if long-term results are the goal to look for. Indeed, only agreements securing all contractors lasting advantages will be able to shift such a goal from vision to sustainable achievement.

On the whole, this strategy would predictably result in support to development of paediatric ARV drug markets in resource-constrained countries while bringing these countries into the overall pharmaceutical market.

TOP MANAGERS’S INSIGHTS INTO INCENTIVE STRATEGIES ALLOWING GENERIC INDUSTRIES TO PRODUCE AFFORDABLE FDC ARVS FOR CHILDREN

Achara Eksaengsri (Deputy Director, Research and Development Institute - Government Pharmaceutical Organization), Thailand: Doses of ARV drugs given to paediatric patients need to be adjusted according to their weights and surface areas [123]. Many children refuse to take large volume of conventional paediatric ARV drugs as such dosage form can cause nausea and vomiting. Therefore, there is a request from physicians from organizations such as UNICEF, WHO, MSF etc to have simplified dosage form of paediatric ARV drugs [128, 133]^{54,55}.

Development of FDC paediatric ARV drugs by generic companies is confronting with the following problems:

⁵⁴ www.who.int/3by5/en/finalreport4Apr.pdf.

⁵⁵ [www.who.int/hiv/pub/guidelines/PaedARTguideDRAFT_webreview NOV05%20_2_.pdf](http://www.who.int/hiv/pub/guidelines/PaedARTguideDRAFT_webreview_NOV05%20_2_.pdf)

⁵³ www.wto.org/english/news_e/pres05_e/pr426_e.htm.

Table 5. Exacerbated Data Exclusivity

Term refers to a practice which temporarily bars registration files of an originator from being used to register the generic copy of a brand-name medicine. As long as fixed time period (five years in the U.S. and eight years in the Europe), Drug Regulatory Authorities are prevented from registering such generic equivalents unless generic producer has carried out independently the required safety and efficacy tests, or bilateral agreements encompassing Voluntary License (VL) use (Table 4) have been undertaken.

Data exclusivity impact does actually consist in barring Compulsory License (CL) use (Table 4) until the expiry of data exclusivity itself and, mainly, in securing research-based companies a monopoly period in countries agreeing to data exclusivity even when a medicine is not patented in the specified country.

Definitely, this practice goes far beyond WTO request for data protection against unfair commercial use only (Table 4).

Table 6. Desano Profile*

Established in 1996, Desano is a dynamic and fast-growing pharmaceutical company with a solid technology foundation. With 10 years development, Desano has become an influential Chinese pharmaceutical enterprise in R&D, manufacturing of APIs, intermediate, formulation and nutritional ingredient especially in field of HIV/AIDS.

Desano has been manufacturing APIs for ARVs since 1999 and is a major API supplier for the world market. The company is producing large volume of ARV APIs including zidovudine, stavudine, lamivudine, didanosine, nevirapine, efavirenz, indinavir, nelfinavir. APIs are exported to India, Thailand, Africa and South America.

Desano, as ARVs manufacturer designated by Chinese government, has also launched generic ARVs in China such as didanosine powder, nevirapine tablet, stavudine, zidovudine, indinavir capsules.

Dedicating itself to the mission of improving the quality of human life by commitment and innovation, Desano will implement ICH (International Conference on Harmonisation of Technical Requirements of Pharmaceuticals for Human Use) and cGMP (current Good Manufacturing Practice) standards, take advantage of specialty in pharmaceutical field, establish its own brand and grow up to be an enterprise with sustainable development in the combat against HIV/AIDS.

*Dr. Li Jin Liang, Vice President for R&D Shanghai Desano Biopharmaceutical Co. Ltd., China (communication to Dr. Dionisio on May 2006: with permission).

1. No conclusion from any international organization regarding the most suitable FDC paediatric ARV drugs.
2. Difficulties in conducting bioequivalence (BE) studies in children. There is a suggestion that data of BE studies in healthy adult volunteer can be used in children, but there is still no consensus on this issue.
3. Economy of scale in the manufacturing of FDC paediatric ARV drugs cannot be achieved as there is very small number of paediatric patients in each country. WHO or international GMP (Good Manufacturing Practice) prequalified manufacturing plants need a large scale production to make up for the cost of entire production.
3. There should be regional procurement from either WHO or UNICEF in order to achieve the economy of scale of production from generic manufacturers.
4. Regarding intellectual property rights (IPRs), WHO should set clear and simplified guideline to implement TRIPs flexibilities including Doha Declaration (Table 4).
5. WHO should set guideline to prevent evergreening patents in developing countries and least developed countries.

Arun Kumar Khanna (Director Operations - Emcure Pharmaceuticals Ltd), India: The developing world urgently needs generic fixed-dose combinations of paediatric ARVs. However, various factors make this unattractive for manufacturers.

Therefore, combined incentives to generic companies to boost manufacturing of affordable FDC paediatric ARV drugs against the backdrop of market unattractiveness and enforced intellectual property rights should be:

1. Consensus agreement on the most suitable FDC paediatric ARV drugs regarding drugs and their doses in such combination.
2. WHO should clearly indicate that BE studies of FDC paediatric ARV drug formulations can be conducted in healthy adult volunteer for those that certain single drugs such as stavudine, zidovudine, lamivudine, nevirapine in which their formulations have already been proven to be safe and used in children.

The “market” for paediatric ARV products is considered small (<1% of adult market) thus severely limiting the return on investments on product development. Low usage for children primarily is due to i) low awareness amongst HIV-infected parents, ii) low awareness on treatment options and paediatric regimens amongst doctors, iii) non-compliance due to non-availability of FDCs for children iv) poor focus on procurement of paediatric ARVs by government, and bureaucratic hurdles, v) almost no facility to care for orphaned infected children, vi) lack of published studies → limited data → low acceptance of new formulations by doctors → low usage → poor “market”. Limitations for conducting clinical trials also arise from non-availability of volunteers in this age group. Further, stringent regulatory requirements for grant of Certificate of Pharmaceutical Product

Table 7. Voluntary License Advantages Over Compulsory License, Differential Pricing and Donation Options

<p>Voluntary Licenses (VLs)</p> <ul style="list-style-type: none"> - suitable for attaining (through technology transfer) technological catch-up while securing transparent relations with research-based companies. - suitable for breaking away from dependence on fickleness and drug price fluctuations by foreign corporations. - suitable for keeping generic drug prices more affordable than those of branded originals even after cutting by patent's owners. - suitable for securing both research-based and generic industries lasting advantages which may include market expansion, economic gains as well as manufacturing and R&D partnerships. - suitable (as per export authorization) for expanding access to affordable ARV drugs in foreign under-served markets lacking capability for domestic manufacturing. - suitable for enhancing manufacturing of appropriate fixed-dose ARV combinations for children. - suitable for achieving, by native language instruction enclosed, the proper use of medicines. - suitable (through making generic copies of new and second-line ARVs really available) for appropriately tackling impending viral resistance expansion in the developing world. - suitable for helping domestic plants for ARVs in sub-Saharan Africa take off and engage in R&D partnerships encompassing technological catch-up, exploitation of TRIPS flexibilities, raised job opportunities, as well as improved marketing power. - suitable for supporting markets development in resource-constrained countries while bringing these countries into the global pharmaceutical market. In economic terms this means as incentive for either research-based or leading generic companies to enter these markets with existing products while concurrently investing in new products for them. <p><i>requirements (under VLS) for effectively expanding access by the poor include: 1) WHO's brokering role in negotiations, 2) substantial incentives to generic firms (i.e. "generics" exclusive bulk purchasing by major donors, fiscal relief by country governments).</i></p> <p>Compulsory Licenses (CLs)</p> <ul style="list-style-type: none"> - frequently feared by governments in the developing world because of risks of blackmail and withdrawal of investments based on multinational corporations and wealthy countries governments would be detracted from profits. - cumbersome and unwieldy frames requiring enabling national legislations already into force. <p>Differential Pricing (Goal: Prices Close to the Manufacturing Cost)</p> <ul style="list-style-type: none"> - promotion of local market by keeping competition with domestic and foreign manufacturers. - support to R&D. - risks that offers are not available in the private sector notwithstanding most people in developing and least developed countries access healthcare through private organisations (lack of transparency). - risks that discounts might preclude the use of "generics" (exclusion from the market of generic competitors: lack of transparency). - risks for drug price fluctuations depending on fickleness and policy strategies of research-based corporations. - drug prices unlikely to be as affordable as those of "generics" domestically manufactured. - risks for diversion and leakage (need to modify packages, formulations and instruction languages). - discounted drugs not always available in every country. - discounted drugs sometimes not registered in specified countries. - cumbersome distribution channels for some discounted medicines. - discounted price quoted by the manufacturers may not constitute the final price for reasons including (though not limited to) exceeding mark-ups and lack of monitoring. <p>Donations</p> <ul style="list-style-type: none"> - no suitability to long-term needs in the developing world where consistency of supply is crucial for chronic conditions. - risks to undermine the development of local markets by locking out competition. - no sustainability: it would be impossible by the patent's owners to give away their products indefinitely.
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(COPP), requirements for bioequivalence/clinical trials discourage investments and initiatives by the pharma industry.

Steps for increasing usage of paediatric ARVs (and hence the "market") are: i) to create awareness of HIV/AIDS so that cases are reported, the patient – the disease – the treatment are all accepted; ii) governments, pharmaceutical industry and NGOs should have defined social responsibility for creating awareness and sensitizing the population; iii) infrastructure to train doctors and disseminate guidelines will

increase the use of paediatric ARVs; iv) governments should have special fund for procuring and distributing free paediatric ARVs [139]⁵⁶ with lesser bureaucratic hurdles; v) availability of appropriate and desirable ARV FDCs.

Besides, WHO should partner with scientific bodies to sponsor/ facilitate studies on paediatric ARVs so that generic manufacturers are guided on formulation and dosage, and

⁵⁶www.who.int/hiv/pub/advocacy/promotingfreeaccess.pdf.

rely more on post-marketing surveillance data for safety and efficacy. Further, regulatory bodies should give relaxation for grant of COPP as compliance to size and number of commercial batches may not be feasible. Governments should waive duties and taxes on paediatric ARV formulations, provide incentives to R&D units through lower tax burden on different counts. Innovators should waive off intellectual property rights on patented molecules to facilitate production of FDCs and encourage generic manufacturers. WHO can facilitate by speedier inclusion of monographs in pharmacopoeia, specifying uniform reference standards and identifying Contract Research Organisations (CROs) for development work. WHO should consider WHO GMP certification of the manufacturing units as sufficient for pre-qualification for supply of paediatric ARV FDCs to developing countries.

Simultaneously, pharmaceutical industry should continuously develop formulations for paediatric use in spite of low commercial gains from the category in addition to various products for adult population suffering from HIV/AIDS.

We at Emcure Pharmaceuticals Limited understand the disease and its enormity, and have taken development of paediatric ARVs including FDCs as a special mission in spite of various limitations and constraints. Emcure's committed efforts resulted in the development of Dual and Triple drug fixed dose formulations apart from a wide range of suitable individual drug formulations for children.

Besides, we are continuously working towards sensitization of the society for acceptance of infected population, disease awareness and its prevention. Also we are setting up exclusive ARV pharmacies, supporting similar initiatives offering cost effective solutions etc.

But considering the spread of the disease and size of the infected population, whatever be the efforts made by Emcure, it would be inadequate unless until the ARV drug manufacturers take initiatives in this direction. Government and regulatory authorities should extend liberal support in all possible ways so that the HIV/AIDS infected paediatric population is treated and rehabilitated.

Krisana Kraisintu (Pharmaceutical Consultant - German Medical Aid Organization-action medeor, Germany; Tanzania Pharmaceutical Industries, Tanzania; Pharmakina, Democratic Republic of Congo-), Thailand: We all know very well why generic companies do not want to manufacture paediatric formulation but I would like to summarise and put forward my incentives for them:

1. Economy of scale can not be achieved. Demands are very low in each country. If products are in syrup form, they will have stability problem so manufacturers will have to reject once they reach expiry dates.

Incentive: Bulk procurement by international organizations or regional procurement in order to achieve economy of scale.

2. Registration process of paediatric products can cause a delay as many data are required by authorities and all need time and efforts with very little return.

Incentive: For products that have already been used in adults and small doses (breaking of tablets) have al-

ready been given, they have been proven to be safe and effective. Pharmacokinetics or BE studies can be done in adult subjects. These products should go through fast track registration. There must be ways to simplify registration process in terms of time and requirements.

3. Governments in developing countries do not envisage the needs for paediatric products.

Incentive: Government should have clear policy to treat paediatric patients. Guideline should be established. Government should subsidise for the loss of manufacturing these products (the same way as in the case of artemether and lumefantrine FDC antimalarial drug "Coartem" by Novartis which is subsidised by Swiss government when sold to poor nations).

4. Poor publicity for the need of paediatric formulation.

Incentive: Public should be informed at all levels.

Sandeep Juneja (HIV Project Head - Ranbaxy Laboratories Ltd), India: Different companies may have different reasons to invest in new formulations to counter HIV infection despite relative unattractiveness of the market and especially the paediatric segment. The reasons may be:

- It is the right thing to do. As majority of the HIV-positive children succumb to AIDS within 2-3 years of their life without antiretroviral therapy (ART), they lose the chance of benefiting from future innovations that may cure the infection or prolong their life substantially. While adults have the option of simple, FDC HAART [126], children have to live with cumbersome and unpalatable single drug options that may adversely impact compliance to therapy. Conscientious pharmaceutical companies in the HIV treatment segment will find it hard to ignore this patient need
- A multi-drug paediatric FDC may be technologically challenging and would address a significant unmet need, hence there is expected to be wide recognition for a company that brings such a drug to market. Some companies may be motivated by international acknowledgement of their efforts
- Paediatrics may be perceived as a niche segment in which some companies may see limited competition and hence greater price stability. Hence, there may be perception of a viable business case of creating a paediatric FDC and selling it in that segment even if at a modest profit which is missing in the adult ART segment

Despite these reasons, it is highly likely that pharmaceutical companies will only pursue provisions in international/national intellectual property (IP) laws for making paediatric FDCs available. This may limit or prevent usage in some highly affected countries but will still make a significant impact in countries without IP constraints, just like the triple FDC ART for adults.

Stavros Nicolaou (Head of Strategic Trade - Aspen Pharmacare Holdings), South Africa:

1. Paediatric ARV FDCs and paediatric ARVs in general have posed immense challenges for the entire

ARV provision, treatment and supply chain, whether it be that of clinicians, dispensers, manufacturers, policy makers or patients.

2. At this point, most paediatric dosage delivery forms consist of liquid solutions, tablets which are crushed into powder and swallowed by patients or a single product which consists of granules which are reconstituted into liquid by the addition of distilled or sterile water.
3. To date, liquid and granule forms for reconstitution have provided extensive practical challenges in resource limited settings. These dosage forms are unstable at the temperatures that exist in the developing and least developed world (where most patients and their families do not own refrigerators) and hence potency of these products is compromised in unstable conditions. In the absence of refrigeration, which is in almost all cases in resource limited settings, the dosage forms prove highly challenging.
4. It is for this reason that clinicians and physicians in resource constrained communities have turned to tablets and more specifically the crushing of tablets in an attempt to achieve paediatric dosage forms, which are then swallowed with water by paediatric patients. Although some lower strength ARV products, such as for example stavudine 15mg, provide paediatric strength dosaging for higher weight band children, those ARVs with higher dose strength tablets have relied on the breaking of tablets into halves and quarters, which provides some element of subjectivity in dosaging (most of the tablets are not scored, leading to uneven distribution on attempting to halve a tablet).
5. The aforementioned challenges are exacerbated by the dosaging flexibility that paediatric dosage forms require. The dosaging of paediatric patients varies between patient masses of 5 to 30kg, where the strength of the ARV increases in increments of every few kilograms of increase in body weight.
6. Whilst the development and provision of paediatric ARVs remains challenging in itself, the challenge is enhanced when one attempts to combine paediatric ARVs into fixed dose combinations, whether they are 2 in 1 or 3 in 1 FDCs.
7. Some have argued that IPR (intellectual property right) restrictions have acted as a disincentive to the formulations and development of FDC ARVs for paediatric use, as they have allegedly acted to restrain formulators from combining various combinations of patent protected molecules, for fear of the legal minefield that patent infringement might present. The particular concern in this instance, is that patent infringement could lead to a court injunction and the removal of products from shelves, ultimately leaving patients in the lurch.

Even for innovator companies, who have patents for some of the molecules that would make up the FDC, unless they have specific co-development agreements with other patentees, they face the same problems as

generic formulators when they attempt to develop combinations which partly contain their own molecule(s).

South Africa, as a country, has been highly innovative in finding mutually expedient solutions in response to the IPR issues, by striking the appropriate balance between rewarding innovation, but at the same time enabling the access of ARVs to resource constrained communities.

Instead of becoming embroiled in controversy and the rising tensions that IPR infringement or compulsory licensing usually realises, South African based innovator companies worked together with their local generic counterparts through the granting of voluntary licenses, which enhanced access and affordability of these products, through authorised generic introduction in developing countries, but at the same time kept the multi-lateral patent system intact. This has expedited generic supply and realised a win-win situation for patentees, generic manufacturers, policy makers and patients and contemporaneously enabled South Africa to uphold all its multi lateral trade obligations. Typical voluntary license agreements, signed in South Africa and extending into Sub Saharan Africa, include those concluded by local SA Manufacturer Aspen with GSK, Boehringer Ingelheim, BMS, Gilead and Merck.

8. What then constitutes the most ideal dosage form for paediatric use? Clearly, whatever this entails, would at very least, aside from the conventional pharmacokinetic and dynamic aspects, have to accommodate the challenges of highly flexible dosaging and stability in resource constrained settings where refrigeration is not readily available. Therefore in consciously addressing the question, "what strategies to boost production of generic fixed-dose antiretroviral drug combinations for children in the developing world?" it is critical to have an appreciation of the combined impact of all those challenges in developing paediatric ARV FDCs. Moreover, in evaluating this question, one should relate the association of paediatric dosage forms and their challenges to market unattractiveness for ARV formulations and developers.
9. It is clear that the ideal type of ARV FDC for paediatric use is one that accommodates the patent and other IPR challenges, provides flexibility in dosaging to accommodate the multitude of weight bands that paediatric patients present, provide sanctity in product stability and potency and provides pharmacokinetic compatibility when combined with other ARV combinations.
10. It is quite possible to formulate and develop FDC paediatric products that collectively accommodate all of these challenges and their associated risks. This risk is exacerbated in the absence of guaranteed and co-ordinated volumes, which is presently the case and would explain the market unattractiveness aspect. To this end, the introduction of any multi-faceted incentives to generic formulators would have to

address some of the risks and in particular the market unattractiveness aspect. In developing incentives to offset the risks, it is important to renew the risks, which include the following:

- The direct and indirect dosage form and formulation R & D costs.
 - Generic ARVs have in recent time been sold on either a cost recovery or forward pricing basis. This means that generic ARV formulations have factored future (hence the term forward pricing) volumes in their existing manufacturing costs in order to discount economies of scale against existing manufacturing costs. Should anticipated volumes not realise, as has been the case with adult forms, this places immense pricing pressure and hence increased risk on the generic formulators. The development of paediatric ARV FDCs could further exacerbate this problem.
 - One of the biggest problems faced by generic manufacturers in the paediatric ARV FDC equation, is that in the absence of an identical FDC ARV, a generic equivalent cannot be developed and registered, as this would involve extensive clinical trials on the part of the generic manufacturer, which are not only highly costly, but require the involvement of specialised clinical skills.
 - The rewards for the development into paediatric ARV products are low and the risks high. The unpredictability of this business provides a further impediment.
11. Whilst the South African experience of voluntary licensing and the technology transfer arrangements through for example the Aspen model, is capable of addressing the IPR restrictions, as described earlier, the incentive strategies that could be successful in mitigating the above risks and triggering a greater interest from generic formulators could include the following:
- The concept of establishing multi-lateral funded private-public partnerships, as exist in alliances such as the development of drugs for neglected diseases, could provide the incentives which could trigger a heightened interest in this very important area of paediatric ARV FDCs by generic formulators.
- In practical terms this would synergistically continue multi-lateral capital funding together with generic formulator R&D, technical and business strategy skills.
- Non-fiscal incentives - eg preferential tax incentives or accelerated depreciation on capital expenditure for capital costs associated to the development.
 - Guaranteed off-takes, advanced purchase commitments and payment terms in order to reduce risk.
 - WTO compliant subsidies by governments.
 - Accelerated registration or harmonisation and mutual recognition of regulatory standards, hence reducing regulatory costs.
 - As muted in an optional reward system for neglected diseases, the establishment of an international reward

authority which would grant revenues to companies taking the risk in the paediatric field.

- The option reward system would propose government or multilateral bodies/philanthropic agencies providing fund financing in order off reward payments to cover the risks of paediatric ARV development, marketing + distribution. This would enable prices to fall to an efficient level.

Aloka Sengupta (Vice President ATM – Strides Arcolab Ltd), India: The “3 x5” global target aims to include infants and children in at least 10-15% of all patients accessing antiretroviral treatment. However, there has been limited progress in this area as the development of paediatric dosage forms entails high outlays particularly with regard to clinical efficacy trials. The generic pharmaceutical industry has displayed a commendable sense of social responsibility in developing fixed dose tablets for children and alternative dosage forms. Much more needs to be done if we are to ensure that gen next leads a healthy productive life. The incentives that generic formulators of ARVs require to take paediatric initiative forward are:

1. Formal collaboration with foundations/NGOs/UN bodies/academic institutes to conduct clinical trials of alternative dosage forms such as dispersible tablets, granules etc
2. Funding from EU/Global Fund etc to encourage development and such trials
3. Greater response from procurement agencies, ministries of health etc – for example few if any of the recent tenders have requirements for paediatric dosage forms. Even if such requirements are there the quantities are too small to be practicable. Perhaps global pooling of requirements would increase the market size and make the segment more attractive
4. Patents – paediatric products should be completely exempted from patents – only this will encourage development of second line products

APPENDIX - PRIORITY WITHIN PRIORITY: FDC PAEDIATRIC ARVS AS ESSENTIAL MEDICINES IN RESOURCE CONSTRAINED SETTINGS⁵⁷

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Fixed-dose combinations (FDCs) are a cocktail of several drugs formulated in a single pill. In antiretroviral therapy (ART), the most commonly prescribed first line combination in developing countries is 3TC/d4T/NVP. Today, almost 80% of the patients that begin treatment in MSF programmes

⁵⁷MSF participation in this joint paper by no means implies endorsement of the views expressed in the sections authored by representatives of organisations other than MSF. The arguments expressed in the sections not authored by MSF in no way represent the views of MSF.

are prescribed FDCs. With one tablet twice per day, it is simple for the patient to take, and simple for health staff of limited training to administer [18]⁵⁸. It does not carry any food restrictions, meaning that it can be taken on an empty stomach. Being in tablet form, it can be easily and discretely carried if the patient needs to travel. FDCs also have a considerable impact in improving a patient's adherence to treatment, as they are very well accepted by patients. In addition, the FDC demonstrated excellent clinical outcomes in a study conducted in Cameroon in 2003 [69]. In MSF's treatment programmes, the implementation of FDCs has been a crucial factor without which scaling-up the number of patients would not have been possible.

For the more than two million children living with HIV/AIDS, of which 660,000 are in urgent need of antiretroviral treatment [5]⁵⁹, the situation is radically different. The difficulties associated with diagnosing an infant in remote settings are vast, but beyond the scope of this paper. Once an infant is diagnosed as HIV positive, care for the child is also fraught with difficulties such as those around formula or breastfeeding, the frequency of medical consultations required, and issues of stigma and discrimination. Importantly, treatment remains a further difficulty, in stark contrast to the situation for adults described above. To a great extent, this difficulty is due to the lack of antiretroviral FDCs for children, and the consequences of this lack will now be outlined.

A first difficulty for treating HIV positive children concerns the complexities of dosages. A child weighing eight kilograms following one of the most common WHO-recommended ART [135]⁶⁰ would need to take every day:

2.5 ml of lamivudine (3TC) syrup
7.5 ml of stavudine (d4T) oral solution
and 6 ml nevirapine syrup (NVP)

This list of three different syrups, each to be given in different amounts, increases the risk of errors in administration, of under-dosing through a child's refusal or spitting, and of non-adherence. Further, as the child grows and gains weight, doses will need to be adjusted, and the amounts of syrups to be taken will increase. In our example above, once the eight kg child reaches 10kg, the amount of lamivudine and stavudine required will double. The dose of nevirapine will have to be calculated in square metres of body surface, which can only be determined through the complex square root or logarithmic calculations and measurement of the child's height. The difficulty for caregivers in learning how to follow a strict daily schedule and administer different medications, each in a different quantity that itself varies as time passes cannot be underestimated.

Further complications come from the particular drug characteristics. Oral stavudine solution for example is only stable at room temperature for 24 hours [18]⁶¹. In settings

were households do not have access to refrigeration, which is the case of the majority of settings where most HIV infected children live, the oral solution may therefore not be used. Syrups also present problems in that they involve taking large volumes, and often taste foul, increasing the likelihood of reduced adherence. Other products do not have thermostable versions, or have short shelf lives. Tablets for adults are not designed for partial intake. Scored tablets designed for partial intake are urgently needed.

Research has shown that non-adherence to prescribed regimens is common, whether the disease is acute or chronic, and whether the patient population is adult or paediatric [122]. For HIV patients, non-adherence is particularly problematic: recent studies indicate that taking ARV at sub-therapeutic levels can lead to the development of symptomatic HIV disease, and/or create drug resistance to some or all of the currently available HIV medications [48, 92].

For antiretroviral treatment to be effective and achieve virological suppression, adherence rates of over 95% are required. The easier a treatment is to take, the greater a patient will comply with it. Adherence issues can therefore be particularly problematic for young children, as they are dependent on their caregivers. The complexity of multiple drug antiretroviral regimens, the foul taste of some products, as well as socio-economic factors outside the scope of this document, all contribute to increase the risks of non-adherence in paediatric HIV patients [121].

In a study looking into adherence from the perspectives of mothers of children living with HIV [124], 27% of the mothers responded that "the medications" were the worst thing for them about their child being HIV positive. This was the most frequent answer, and indicates how widespread the negative emotional impact the medications have. Although very few studies looking into the issue of adherence in children exist in the literature [6, 49, 53], factors that are commonly reported as influencing it negatively are complexity of treatment, poor palatability and interference with daily life. These are unfortunately classic characteristics of what paediatric HIV treatment is today in the absence of FDCs.

Stigma also has a considerable impact. 48% of the mothers in the abovementioned study provided an account of a stigma experience during the interview, and 65% feared that they or their child might be stigmatized at some future time. Mothers and other caregivers coming out of clinics providing HIV care and treatment are easily distinguished and pointed out as they carry bags full of ARV syrups and tins of infant formula milk powder. Strict dosing schedules also interfere with daily routines of playing, eating and studying, and put children and their families at risk of an unwanted or inappropriate disclosure. At certain ages, children also begin to question why are they receiving treatment - in some cases not disclosing to children once they ask about their medication creates problems for adherence practices.

The situation described above - of complex dosing, poor palatability, inadequate drug characteristics, all of which have knock-on impacts on stigma and adherence - is not likely to improve in the near future. Pharmaceutical companies are not investing sufficient resources in the development of paediatric formulations. From a commercial perspective, the success in rich countries of methods of prevention of

⁵⁸http://www.bms.com/cgi-bin/anybin.pl?sql=select%20PPI%20from%20TB_PRODUCT_PPI%20where%20PPI_SEQ=22&key=PPI.

⁵⁹www.unaids.org/epi/2005/doc/EPIupdate2005_pdf_en/epi-update2005_en.pdf.

⁶⁰<http://www.who.int/3by5/en/finalreport4Apr.pdf>.

⁶¹http://www.bms.com/cgi-bin/anybin.pl?sql=select%20PPI%20from%20TB_PRODUCT_PPI%20where%20PPI_SEQ=22&key=PPI.

mother to child transmission, and the availability of refrigeration or of formula milk means the market for paediatric antiretrovirals is gradually diminishing in importance. Without a lucrative market, companies are not allocating enough resources to make quick progress. Table 8 shows the paucity of current commercial production of paediatric ARVs in fixed-dosed combinations.

Table 8*.

Company	FDC available in adult version	Is a paediatric version being developed?
Cipla	d4T/3TC/NVP	Yes
	d4T/3TC	Not
	AZT/3TC	Not
	AZT/3TC/NVP	Not
	LPV/r	Not
Hetero	d4T/3TC/NVP	Not
	d4T/3TC	Not
	AZT/3TC	Not
	AZT/3TC/NVP	Not
	LPV/r	Not
Aurobindo	d4T/3TC/NVP	Not
	d4T/3TC	Not
	AZT/3TC	Not
	AZT/3TC/NVP	Not
	LPV/r	Not
Strides	d4T/3TC/NVP	Yes
GSK	ABC/3TC	Not
	AZT/3TC	Not
Abbott	LPV/r	Not
Gilead	TDF/FTC	Not
Ranbaxy	d4T/3TC/NVP	Yes
	d4T/3TC	Yes
	AZT/3TC	Not
	AZT/3TC/NVP	Not

*The list is not extensive and other companies are working on adult and paediatric FDCs.

Unless there is increased pressure on drug manufacturers, including intervention from UN bodies and governments, these therapies will not be made available [73, 74]^{62,63}. Yet this pressure does not exist. WHO has released at the 2006 IAS Conference in Toronto the standardized dosing tables that have been eagerly awaited since 2003 [26, 136]⁶⁴. These tables were produced using the available pre-qualified mole-

cules for adults including an adult FDC of d4T/3TC/NVP and are still fairly complex and reinforce the fact that adult formulations are not appropriate for use in small children. In fact, in the absence of more clear recommendations, producers do not have a clear signal on which products they should develop. As an illustration of the kind of problems this lack of recommendations can cause, the only two existing FDCs are different in dosing. Doctors and other health professionals have still no simple guidelines for treatment of HIV in children. Unless clear dosing recommendations are urgently developed by experts and validated by international bodies like WHO and UNICEF, and the pre-qualification of FDCs for paediatric use accelerated, it is very unlikely that the few companies producing child adapted formulations will be encouraged to develop new or improved products. Pressure is also needed so that children can access all existing products. More studies are urgently required for example on the safety of medications like efavirenz for use in paediatric populations. Today, due to a lack of data, the drug cannot be used in younger children or those weighing less than 10 kg [143]. Of the 60,000 patients currently receiving ART in MSF programmes around the world, 3,000 of them are children less than 15 years of age. MSF experience proves that treatment works and that it can be delivered in resource-poor settings, achieving outcomes comparable to those seen in developed countries. As in the case of adults, treatment outcomes are very good [71, 72] in these children, with comfortable dosing schedules and no food restrictions. It is therefore quite possible that smaller children could benefit from these advantages if a FDC in paediatric smaller dosages were available. Until paediatric FDCs are produced, however, scaling up programmes to reach more children will not be possible. In some MSF projects when no other choice is available, adult fixed dosed combination scored tablets are split in two to provide antiretroviral treatment for children in need of it. Resorting to this unsatisfactory method still limits the number of children that can be given FDCs to those that weigh 10 kg and above. Even assuming paediatric FDCs are developed, syrups will still be needed for infants, and for those children who have any contraindication or are not responding to the antiretrovirals contained in a FDC.

The term "Essential Medicines" is used to describe forms of medication fundamental in providing basic care [127]⁶⁵. Essential medicines are those that satisfy the priority health needs of the population. Selected according to their public health relevance, evidence of their efficacy and safety and comparative cost effectiveness, they are intended to be available within the context of functional health systems at all times in adequate amounts, in adequate dosage forms, with assured quality and at a price the individual and the community can afford [127]⁶⁵. Paediatric antiretroviral treatment, despite its undoubted importance and the ethical obligation to provide life saving treatment to this neglected portion of the population, is not available under this criteria. As research and development priorities continue to be driven by market and not by patient needs, and while we wait for the development of urgently needed paediatric FDCs, millions of HIV positive babies are dying before they reach their second birthday.

⁶²<http://www.accessmedmsf.org/prod/publications.asp?scntid=28112005640255&contenttype=PARA&#top> [last access 2006 February].

⁶³<http://www.accessmedmsf.org/documents/BKKconferencebriefingdocument.pdf> [last access 2005 December].

⁶⁴<http://www.cipladoc.com/therapeutic/admin.php?mode=prod&action=disp&id=160> [last access 2006 February].

⁶⁵http://www.who.int/medicines/services/essmedicines_def/en/.

AUTHORS CONTRIBUTIONS

D. Dionisio conceived, designed and coordinated the study. Individually authored contributions by each co-author are specified as follows:

R. Gass and P. McDermott: *Stepping up action for children to be included in appropriate ARV treatment regimens*. V. Racalbutto, M. Madeo and G. Braghieri: *Actions to promote paediatric antiretroviral treatment as a challenge for developing countries health services: considerations based on the cases of Uganda and Ethiopia*. S. Crowley: *Preferred ARV treatment options for children: making sure the children are not left behind in treatment scale up*.

E. Dos Santos Pinheiro, P. Graaff and A. Vasan: *Reshaping awareness of needs: are reliable data for production and demand forecasting of FDC paediatric ARVs actually lacking?* A. Eksaengsri: *Thai GPO's way forward to scale up access to FDC paediatric ARVs*. H. Moller: *How to implement strategies to enhance development, production, affordability and appropriate supply systems of suitable ARV drug paediatric formulations?*

D. Dionisio: *Combination incentives to generic companies to boost manufacturing of affordable FDC paediatric ARVs against market unattractiveness and enforced intellectual property rights*. A. Kumar Khanna, K. Kraissintu, S. Juneja, S. Nicolaou, A. Sengupta and A. Eksaengsri: *Top managers's insights into incentive strategies allowing generic industries to produce affordable FDC ARVs for children*.

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CONFLICT OF INTEREST STATEMENT

None declared.

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