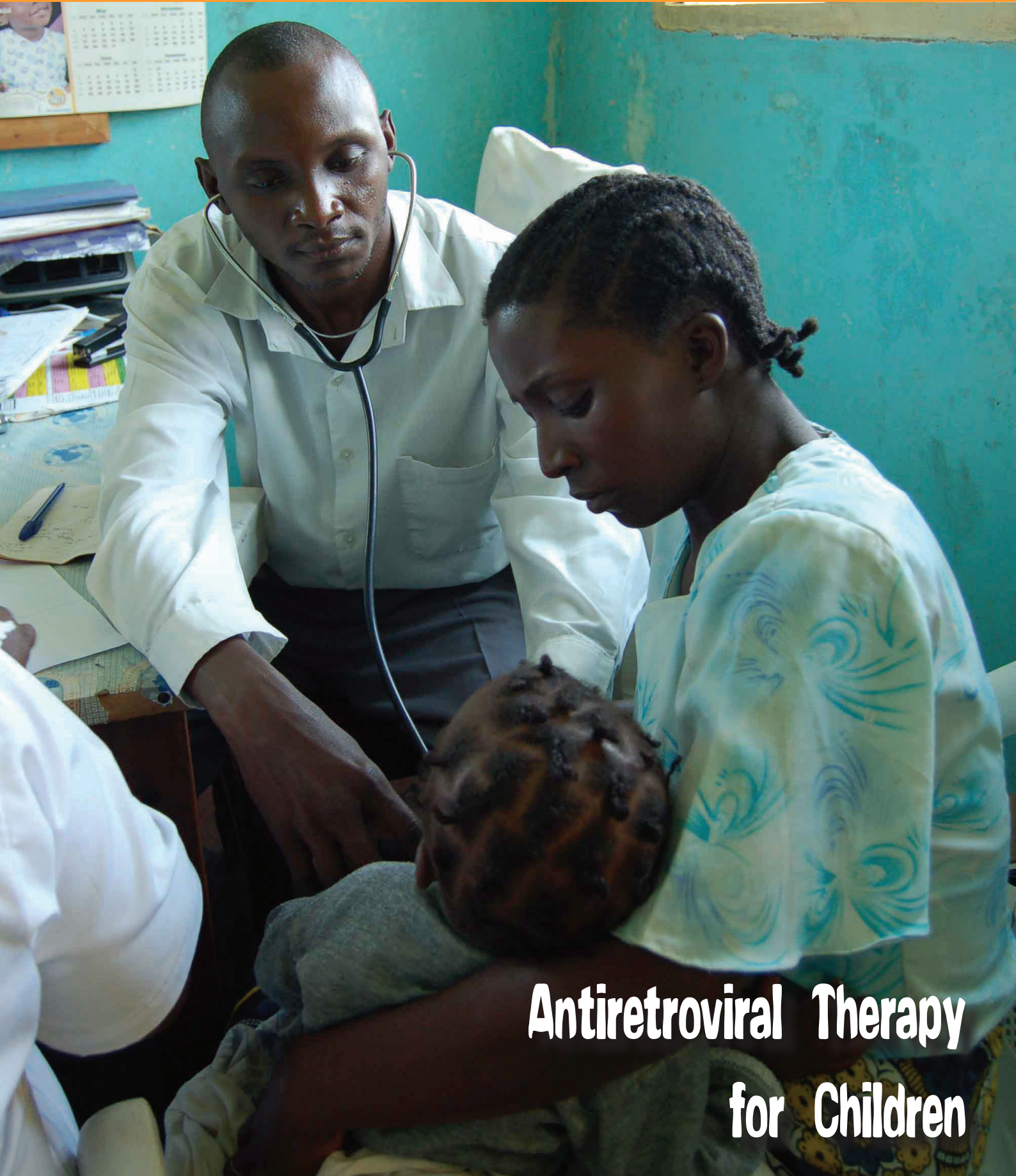


Pharmalink

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**Antiretroviral Therapy
for Children**

About the Cover Photo



Peter a clinical officer treats a patient at the Gongoni health centre in Malindi, Kenya, July 2007. Allan Gichingi/IRIN

About Ecumenical Pharmaceutical Network (EPN)

Ecumenical Pharmaceutical Network (EPN), a former programme of the World Council of Churches (WCC) with membership in over 30 countries, is a non-profit Christian organisation that works to support churches and church health systems provide and promote just and compassionate quality pharmaceutical services.

Vision

A valued global partner for just compassionate quality pharmaceutical services for all

Mission

To support churches and church health system provide and promote just and compassionate quality pharmaceutical services.

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About this Issue

Ecumenical Pharmaceutical Network (EPN) members have highlighted the issue of lack of access to medicines for children and are joining other like-minded people and groups to address this issue. As part of this process, we are pleased to share with you this issue of *Pharmalink* newsletter which in order to provide more insights especially for health workers who are involved in paediatric treatment, explores the issue of **Antiretroviral Treatment for Children**.

As children's bodies are constantly changing, drug doses need to be altered to make sure that a child is not given too much, or too little, of a drug. Information about specific drugs is often limited, and drug manufacturers and expert guidelines use a variety of ways to calculate doses of paediatric ARVs, so there is no uniform dosing system to follow. Because of the complex nature of paediatric dosing, under- or over-dosing can be a serious risk. Dosing is further complicated by the variety of forms that ARVs may take when provided to children, all of which require different measurements.

It is our hope this publication will help to address some of these issues. It is also important to note that this field is constantly changing and therefore it is crucial for practitioners to keep a look out for possible changes.

Read on!



Manthabiseng Matthews holds the anti-retroviral treatment medicine for her granddaughter Limpho in her hand, Lesotho, 20 June 2007. Eva-Lotta Jansson/IRIN

Antiretroviral Therapy for Children

Catherine Truman & Sujith J Chandy
Additional information provided by Edwin Barasa and Nathaniel Smith

HIV burden among children

The number of children who have HIV continues to grow. Recent estimates from UNAIDS suggest that globally about 2.1 million [1.9 million - 2.4 million] children younger than 15 years of age have HIV, about 90% of whom live in Sub-Saharan Africa (1).

HIV infection follows a more aggressive course among infants and children than among adults, with 30% dying by 1 year and 50% by 2 years of age without access to life-saving drugs, including antiretroviral therapy and preventive interventions such as co-trimoxazole.

How effective is antiretroviral (ARV) treatment in children?

Studies have shown that antiretroviral treatment reduces illness and mortality among children living with HIV in much the same way that it does among adults. A trial in the United States, for example, found that the mortality rate among a sample of infected children was reduced from 5.3% to 0.7% per year after antiretroviral treatment was made widely available(2). Similar results have been found in developing countries. A study released in 2007, which monitored 586 HIV-positive children receiving antiretroviral treatment in 14 different Asian and African countries, found that 82% were still alive after 2 years (3). WHO has published

technical guidelines outlining antiretroviral therapy care for infants and children, which have been recently updated (4).

Starting antiretroviral treatment in children

As with adults there is an ongoing debate about the best time to start antiretroviral treatment in HIV-positive children. This involves balancing the benefits of improving the child's immune function with concerns about long-term resistance and drug side effects, if treatment is started too early. However most agree that the risk of progression in HIV-positive infants under the age of 1 year is so high that they should be offered ARVs.

The issue of when to start ART in pediatrics is very critical, and recommendations for when to start and what criteria to use can be drawn from the target country guidelines. For example in Kenya, the guidelines are that:

- All HIV exposed infants should be offered routine DNA PCR testing at the 6 week immunization visit. All infants and young children whose HIV exposure status is not known at the time of the first visit to the health facility should be offered antibody based routine testing and advised on infant feeding options, as appropriate.
- Wherever possible, it is recommended that children whose parents or siblings are enrolled in HIV care should be offered HIV testing as a standard of care.
- All children aged less than 18 months with confirmed HIV positive by DNA-PCR should be initiated on ART regardless of CD4 count or percentage, and regardless of their WHO clinical stage.
- Initiation of HAART for children older than 18 months should be based on WHO clinical staging and or CD4 as indicated below

AGE	<18 months	18-59 Months	5-12 Years
CD4%	ALL	<25	<20
CD4 Count	ALL	<1000	< 350
WHO stage	ALL	3 and 4	3 and 4

Which antiretroviral drugs should be used?

As with adults, antiretroviral therapy with at least three drugs is recommended when treating children, because this prevents HIV from becoming resistant to any single drug. It is usually recommended that this therapy should consist of two nucleoside reverse transcriptase inhibitors (NRTIs) combined with either one non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI). For children under 3 years of age, the NNRTI used is usually nevirapine, due to a lack of dosing information for efavirenz.

In resource-poor communities, NRTI/NNRTI-based combinations are recommended over other combinations due to their relatively low cost and the availability of appropriate generic drugs. World Health Organization (WHO) guidelines for resource-poor communities do not recommend the use of protease inhibitors for initial therapy, because it is felt that they should be saved for second-line treatment, if needed.

The WHO recommends that in resource-poor communities, the two NRTIs should include 3TC (lamivudine), combined with AZT (zidovudine), D4T (stavudine), or ABC (abacavir). Considerations about medications that the mother may have received during pregnancy, the toxicity of certain drugs, and whether the child is still being breastfed, all need to be taken into account when choosing a regimen(5). The decision should again be based on the national recommendations of the country. One must pay attention to new developments as there are frequent changes. For example in 2008, the Kenya government updated its recommendations as follows:

“All infants and children being newly initiated on ART henceforth should be started on new recommended national first line ART regimens as outlined in the following table.”

	1 st Line	2 nd Line
Preferred	ABC+ 3TC + NNRTI	AZT + 3TC + PI/r
Alternative	AZT + 3TC + NNRTI	ABC + DDI + PI/r
NVP exposed	ABC + 3TC + PI/r	Refer to senior clinician
	AZT + 3TC + PI/r	Refer to senior clinician



Commonly used paediatric formulations

Side effects

Children receiving ARVs can suffer from the same side effects that adults experience. Because children's bodies are still developing, and they are likely to be exposed to treatment for prolonged periods of time, they may be particularly vulnerable to certain complications(6). Care should, however, be taken to exclude other possible causes of these adverse events before it is concluded that they are a result of ARVs.

Moderate or severe side effects may require drug substitution, or in certain cases ARVs may need to be stopped until the child has stabilized. For example, a child who develops severe anemia due to AZT should be switched from AZT to ABC or D4T. In general, mild side effects do not require such changes, and symptomatic treatment for the side effects may be given (7).

Fixed Dose Combinations (FDCs)

Simplified treatment with a range of FDCs of ARVs that require only one or two pills twice a day make it easier to treat HIV in adults. They reduce the pill burden, are cheaper than separate tablets and are easier to distribute on a national level. However the development of FDCs for children has lagged behind. So despite WHO simplified treatment guidelines that specify which drugs to use in children, countries have had difficulty in getting simple and affordable combinations of the drugs.

In areas where there is a lack of affordable paediatric ARV formulations, clinicians often have no choice but to divide adult FDCs into measures appropriate for children. This carries a risk of under- or over-dosing (8). The WHO

supports this practice only in situations where no appropriate paediatric medications are available (9).

Drugs that come in a powdered form or dispersible tablets need to be mixed with water, so they can only be used if clean drinking water is readily available. Syrups generally have a short shelf-life and often need to be refrigerated after opening, which requires the family to have a large enough refrigerator with a reliable electricity supply.

Treating children may be technically complicated

The dose of antiretroviral drugs given to children is generally based on either weight or body surface area. As children's bodies are constantly changing, drug doses need to be altered to make sure that a child is not given too much (overdosing) or too little (underdosing) of a drug. For example, children under the age of 6 years metabolise certain drugs, such as nevirapine and lopinavir/ritonavir (Kaletra) faster than adults, so even after adjusting for body weight, they may need to be given higher doses to achieve the same effect that the drugs would have in adults.

Recent WHO publications on ARV dosing in children include: *Revised treatment recommendation for infants* (April 2008) and *Updated recommendations on ideal ARV formulations for children* (March 2008). Other WHO documents include: *"Antiretrovirals in Pediatric Patients: appropriate dosing, adverse effects and efficacy (4)"*

Adherence issues

Children on HAART will need to take ARVs every day for the rest of their lives. If they are taken inconsistently, HIV may become resistant to the therapy. Some paediatric drugs have unpleasant taste, or may cause adverse side effects, so children may be reluctant to take their medications. This can put an enormous strain on the daily lives of caregivers, especially when the ARVs need to be taken with food, and they are trying to provide a meal and administer drugs simultaneously. Due to the stigma surrounding HIV, parents and caregivers may be reluctant to fill prescriptions in their local community, or may not make a child's school aware of the HIV status. If so, the child may miss drug doses during the school day. Caregivers may also hesitate to give ARVs if

other people are present when a dose is due. As more fixed-dose combinations appropriate for use in children become available, it is likely that adherence should generally improve, since the pill burden will be reduced.

If a child is non-adherent and develops drug resistance, he/she will need to start second-line drugs. Without second-line therapy, children who become resistant to ARVs face a high risk of illness and death.

Challenges of Antiretroviral therapy for children

- Not all ARVs in current WHO guidelines for children are currently manufactured or are available in formulations suitable, palatable, acceptable or feasible for use in paediatric populations. Guidance on dosage adjustments for weight and age is not yet available for all recommended ARVs .
- There is a lack of data on distribution, metabolism and efficacy for many ARV drugs in children.
- Few FDCs are available in paediatric formulations.
- Costs for paediatric formulations have been well above the reduced prices achieved for adult ARV formulations.

What has the world done to combat these challenges?

- The "3 by 5" global project aims for children to be at least 10-15% of all patients accessing ART.
- In 2004, WHO and UNICEF held a technical consultation: "Improving Access to Appropriate Paediatric ARV Formulations." As a result, companies began to develop appropriate ARV formulations.
- In December 2006, the Clinton Foundation (founded by former U.S. President Bill Clinton) announced that it had negotiated price reductions for paediatric drug formulations made by two Indian pharmaceutical companies. Under this agreement, 19 different ARVs that can be used in children will be produced and made available at the low price of 19 U.S. cents

per day. This will make them 45% cheaper than previously available drugs. As a result of this agreement, the number of children receiving treatment is likely to rise significantly in the 62 developing countries where the drugs are being made available (10).

- In 2008 generic fixed-dose combinations become available for children. In June a fixed-dose combination (FDC) dispersible tablet of lamivudine (3TC) + nevirapine (NVP) + stavudine (d4T) in two different strengths (30 + 50 + 6mg and 60 + 100 + 12mg) for paediatric treatment was launched by Cipla (India).

Currently available paediatric formulations (in India) include:

- Abacavir 20mg/ml solution
- Didanosine chewable tablets 25mg/ 50mg/ 100mg/150mg/ 300mg
- Efavirenz capsules 50mg/100mg/200mg/ 400mg
- Lamivudine 50mg/5ml solution
- Nelfinavir 50mg/ml syrup
- Nevirapine 50mg/5ml suspension
- Stavudine 1mg/ml solution and capsules 15mg/ 20mg/ 30mg
- Zidovudine 50mg/5ml syrup and 100mg capsules
- Lamivudine + nevirapine + stavudine (30 + 50 + 6mg and 60 + 100 + 12mg) dispersible tablets
- Lamivudine + stavudine (30 + 6mg and 60 + 12mg) dispersible tablets

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