

# HATiP

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# Treatment for children

By Carole Leach-Lemens

## Contributors and reviewers

### Reviewers for this edition:

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## Key points

- **Disease progression in untreated HIV-infected children is rapid with over 50% dying before they reach two years of age.**
- **The World Health Organization (WHO) now recommends<sup>1</sup> quick diagnosis and the immediate treatment of all HIV-infected infants and children under two years of age.**
- **Where treatment cannot be provided immediately to children who need it, co-trimoxazole preventive therapy is essential. It is effective as a prophylaxis against opportunistic infections including tuberculosis.**
- **An estimated 38% of children eligible for antiretroviral treatment were receiving it by the end of 2008 under previous WHO recommendations. Treatment coverage is likely to be considerably lower once these new recommendations are taken into account.**
- **Treatment cannot take place in a vacuum. Treatment success requires assessment of: social and economic criteria including nutrition, food security, access to clean water and; the ability and capability of the caregiver (including the provision of education and support) is critical for adherence and integral to effective treatment.**
- **Children respond remarkably well to treatment. The simplification and cost-effectiveness of fixed dose combinations (FDCs) and use of the World Health Organization's (WHO) simple weight band dosing tables counter many of the apparent challenges to getting more children on treatment.**
- **The limited availability and cost of some formulations for children can make the provision of effective treatment more challenging in some settings. Creative solutions have been found. For example, in Malawi ¼ and ½ tablets of Triomune are being used to dose FDCs for children; methods to split paediatric FDCs to doses for children under six kilogrammes have also been devised.**

- **Children are not little adults – treatment is more complex and adherence problems are more complicated than in adults.**
- **Children, with or without HIV infection, often do not like taking medicine; they have difficulties in swallowing pills and the bad taste of some (lopinavir/ritonavir) will make them spit them out or just not want to take the medicines.**
- **A limited or interrupted power supply can preclude refrigeration of some syrups.**
- **Growth requires frequent change of dosage – body changes mean the ability to absorb and metabolise medications changes with growth. Close monitoring is critical, in particular in infants under one year of age where monthly changes in dosage may be needed (but only if weight changes are significant enough to warrant such a change).**
- **Children who become infected despite nevirapine prophylaxis are at risk of developing non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance, further limiting treatment options. The public health approach to scale up of antiretroviral therapy in resource-poor settings is dependent upon NNRTI-based regimens.**
- **A lopinavir/ritonavir (protease inhibitor) based-regimen is the preferred choice for those with prior nevirapine exposure yet its cost and availability preclude widespread use. And, those who fail or do not tolerate this option have few alternatives.**
- **Difficulties in diagnosing tuberculosis in children coupled with drug-drug interaction (for example lopinavir/ritonavir and rifampicin) of treating those co-infected underscores the critical need for developing better options to prevent and treat both infections.**
- **There is a dearth of health care workers experienced and confident in treating infants and children. Training and sensitizing such workers to paediatric HIV has been shown to be an effective intervention to address the problem. However, the shortage of health care professionals in general, and the need to task shift**  
<http://www.aidsmap.com/en/news/0A5FEF7C-C715-4260-AD3F-D12438F03C95.asp> in HIV antiretroviral treatment remain critical.

## New WHO guidelines on antiretroviral treatment for children

The new WHO guidelines, published this month, recommend that all children and infants with HIV under two years of age receive antiretroviral treatment regardless of their CD4 count or disease stage. The guidelines emphasise the importance of early diagnosis of HIV-infection with the fast-tracking of positive results to mother and child.

The continuing challenges of preventing mother-to-child transmission (PMTCT), while not within the scope of this article,

provide the context in which more than 400,000 children continue to be infected each year.

“Even in countries that are rapidly scaling up PMTCT services, the major challenge is to provide more effective antiretroviral interventions, including the provision of antiretroviral treatment for pregnant women and mothers eligible for treatment and to demonstrate the impact of these interventions by a decrease in paediatric infections, HIV-free survival, and improved maternal and child health.”<sup>2</sup>

Clearly, much remains to be done including expanding HIV counselling and testing so that all mothers (and pregnant women) have access to antiretroviral treatment; governments commit to the provision of safe delivery in facilities and ensure the provision of accurate infant feeding information.<sup>3</sup>

Yet significant progress has been made. In 2008 45% of the estimated HIV-infected pregnant women in low- and middle- income countries received some form of antiretroviral treatment, up from 10% in 2004. The expansion of provider-initiated testing and counselling in antenatal clinics, labour and delivery centres and other health care settings is a significant factor in improved coverage.<sup>4</sup>

Evidence-based strategic approaches for PMTCT scale-up [that have proved successful in resource-limited settings](#) include: decentralisation, health-system strengthening and integration within maternal, newborn and child health services, scaling-up innovative service delivery, (for example, use of mobile technology and motor-bikes) and making community-based interventions an integral part of national scale-up plans.<sup>5</sup>

Nevertheless an estimated 730,000 children were living with HIV in 2008, the vast majority in sub-Saharan Africa.

Under the previous WHO guidelines an estimated 276,000 (38%) of children were receiving antiretroviral treatment, up from 127,300 in 2006. The expansion of treatment eligibility under the new guidelines means that the numbers in need of treatment will inevitably rise.<sup>6</sup>

## Which children qualify for treatment?

35% of children with untreated HIV infection will die before their first birthday with over 50% dying before they reach the age of two.<sup>7</sup>

The high risks of rapid disease progression and high rates of mortality in HIV-infected infants and the preliminary results<sup>8,9</sup> of the ongoing Children with HIV Early Antiretroviral Therapy (CHER) landmark study have led the World Health Organization (WHO) to recommend immediate treatment for all HIV-infected children under the age of two.

Studies in resource-rich settings have shown the link between starting ART in infants under six months of age and a reduction in opportunistic infections, death and developmental problems.<sup>10,11,12,13</sup>

The CHER study, conducted in Johannesburg and Cape Town, South Africa, demonstrated that starting antiretroviral therapy in infants at a median age of seven weeks reduced the death rate from 16% to 4% during a follow-up period of 32 weeks compared to those where treatment was delayed (standard of care) representing a 76 percent reduction in infant deaths in the immediate treatment arm.

Those with delayed treatment showed a rapid disease progression and sudden death. In both groups the death rate was highest in the first<sup>13</sup> weeks and decreased thereafter. Failure to thrive was common in both groups, while only opportunistic infections that included pneumocystis jiroveci pneumonia,

cytomegalovirus and oesophageal candidiasis were seen in the group where treatment was deferred.<sup>14</sup>

The World Health Organization's [June 2010 recommendations](#)<sup>15</sup> for starting treatment when access to laboratory testing is possible are:

### CD4 thresholds for starting antiretroviral treatment in children, WHO guidelines, 2010

Age-specific CD4 Threshold for starting ART	<24 months	24-59 months	≥ 5 years
% CD4	All	<25% (clinical stage 3, 4)	(clinical stage 3, 4)
CD4 absolute count	All	<750cells/mm <sup>3</sup>	<350 cells/mm <sup>3</sup>

Early infant diagnosis is essential for early diagnosis and referral to treatment. (See [HATIP January 2008](#) for further discussion of the different methods of early diagnosis and examples of programmatic implementation).

### The use of clinical staging

The use of clinical staging of HIV infection in children is important to:

- Strengthen a clinical diagnosis in the absence or delay of laboratory testing
- Determine the eligibility of children who may not qualify immunologically for ART as well as help to manage treatment
- Determine when to start treatment when there is a discrepancy between CD4 cell count and CD4 percentage –that is when one marker is below the threshold and the other above. David Dunn and colleagues found “CD4 percentage has no or little prognostic value over and above that contained in CD4 cell count” in deciding when to start ART in HIV-infected children<sup>16</sup> even though, this appears to be counter intuitive (since there is greater stability in CD4 percentage). Of particular interest they note the “practical implication is that a CD4 cell count below a treatment threshold (when a CD4 percentage is above the threshold) provides a stronger impetus for starting ART than vice versa.” Such “findings” they add “inform the debate on CD4 cell monitoring in resource-limited settings, since the cheaper and simpler technologies which have been developed usually estimate CD4 cell count but not CD4 percentage”. Dr. Karyn Moshal notes, “for practical purposes, if the child falls in stage 3 or 4, the CD4 count and percentage are irrelevant in making a decision to treat.”

WHO recommends using clinical staging to make a presumptive clinical diagnosis. WHO does not recommend using this as a guide by those not trained in HIV care or the administration of ART.

WHO Clinical stages are classified from stages 1 to 4 corresponding to a progression from asymptomatic to mild, advanced and severe HIV/AIDS. (See Appendix A for a list of illnesses related to each clinical stage)

### WHO criteria for presumptive diagnosis of severe HIV disease in infants and children aged under 18 months where virological testing is unavailable

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A presumptive diagnosis of severe HIV disease should be made if:

The infant is confirmed as being HIV antibody-positive

And

Diagnosis of any AIDS-indicator condition can be made

Or

The infant is symptomatic with two or more of the following:

- Oral thrush
- Severe pneumonia
- Severe sepsis

Other factors according to WHO that support diagnosis include:

- Advanced HIV disease in the mother or recent HIV-related maternal death
- CD4 percentage under 20

### Clinical signs that may suggest HIV infection

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While certain conditions are listed under WHO clinical stages 2, 3 and 4 Houghton and Ball find it helpful in accordance with the South African Guidelines for the Management of HIV in Children<sup>19</sup> to distinguish among signs and conditions that may suggest HIV infection and are seen primarily in those children and infants who are HIV-infected

- conditions that are seen in both HIV- infected and uninfected children and infants, and those
- specific to HIV-infection.

1. Other clinical signs or conditions that may suggest HIV-infection, common in HIV-infected infants and children but not in those uninfected.	<ul style="list-style-type: none"> <li>● Severe pneumonia</li> <li>● Severe bacterial infections especially if recurrent</li> <li>● Persistent or recurrent oral thrush</li> <li>● Bilateral painless parotid swelling</li> <li>● Generalised lymphadenopathy other than inguinal (in the groin area)</li> <li>● Hepatosplenomegaly</li> <li>● Persistent or recurrent fever</li> <li>● Neurological dysfunction</li> <li>● Herpes zoster – a single dermatome (nerve root)</li> <li>● Persistent generalised dermatitis that does not respond to treatment.</li> </ul>
2. Other clinical signs or conditions common in HIV-infected but also common in ill uninfected	<ul style="list-style-type: none"> <li>● Anaemia</li> <li>● Chronic ear infection</li> <li>● Persistent or recurrent diarrhoea</li> <li>● Severe pneumonia</li> <li>● Tuberculosis</li> </ul>

	<ul style="list-style-type: none"> <li>● Bronchiectasis</li> <li>● Failure to thrive</li> <li>● Marasmus (one of three form of serious protein-energy malnutrition occurring in young children mainly in resource poor settings at the time of weaning)</li> </ul>
3. Signs and conditions specific to HIV infection	<ul style="list-style-type: none"> <li>● Pneumocystis jiroveci pneumonia</li> <li>● Oesophageal candidiasis</li> <li>● Invasive salmonella infection (not specific to HIV-infected children in parts of southern and eastern Africa. Non-typhi salmonella is a common cause of bacteria in infected and uninfected children in some countries)</li> <li>● Lymphoid interstitial pneumonitis</li> <li>● Herpes zoster affecting several nerve routes (dermatomes)</li> <li>● Kaposi's sarcoma</li> <li>● Rectovaginal or rectovesical fistula (specific to Africa region)</li> </ul>

In summary WHO recommends

- starting ART in all HIV-infected infants and children under 2 years of age irrespective of CD4 count or WHO clinical stage;
- starting ART for all HIV-infected children between 2 and 5 years of age with CD4 counts of  $\leq 750$  cells/mm<sup>3</sup> or %CD4+  $\leq 25\%$ , whichever is lower irrespective of WHO clinical stage
- starting ART for all HIV-infected children more than 5 years of age with a CD4 count of  $\leq 350$  cells/mm<sup>3</sup> (as in adults), irrespective of WHO clinical stage
- starting ART for all HIV-infected children with WHO paediatric clinical stage 3 and 4 disease irrespective of CD4 cell count;
- starting ART for any child less than 18 months of age who has been given a presumptive clinical diagnosis of HIV infection

South African guidelines recommend the 'fast tracking' (within two weeks) of children on to ART for any child with stage 4 disease and any child with MDR/XDR TB.<sup>20</sup>

For treatment to be effective good adherence is essential. Consideration of an infant's or child's eligibility for antiretroviral treatment cannot be separated from vital social criteria. That is, treatment does not exist in a vacuum.

South African guidelines recommend the following criteria:

- At least one identifiable and prepared caregiver who is committed to administering ART as prescribed and is willing and able to attend all associated appointments
- Where possible disclosure to at least one other family member within the household for an alternative responsible caregiver in the absence of the mother
- Aim for all potential treatment supporters to be assessed for understanding and commitment



- Assessment of other family health needs (including antiretrovirals) is advised, because success of the child is dependent upon the health of their caregivers.<sup>21</sup>

These criteria are explored further later.

## Which drugs?

### Challenges in treatment of children

Until recently treatment for infants and children was very difficult due to the lack of paediatric formulations suitable for use in low and middle-income countries. In the past four years a number of companies have developed important fixed-dose products which go some way to simplifying treatment for children.

"It can be done. It can be simplified and [treatment] has to get down to grass-roots levels. PMTCT [coverage] has to go up. [The question is] how to make something complex relatively simple." says Professor Diana Gibb of the United Kingdom's Medical Research Council. She has led some of the most important studies of paediatric HIV care, including the CHAP study of cotrimoxazole preventive treatment.

"The fantastic response to ART in children, coupled with the simplification of dosing using fixed-dose combination baby tablets (data now exists about these being preferred [to syrups] in even very young children), and simple weight band dosing tables have helped a lot," she adds.<sup>22</sup>

Until recently the only antiretroviral products available for treatment of children and infants were liquids, or powders that had to be reconstituted with water, requiring clean water, careful measurement and, in some cases, refrigeration.

d4T+3TC+NVP, available in a fixed-dose combination (FDC) for adults as well as children, is known as *Triomune*, *Triomune Junior* and *Triomune Baby*, respectively. Since children metabolise nevirapine faster than adults these formulations provide increased doses of nevirapine relative to the adult dosing. *Triomune Baby* combines 50 mg nevirapine, 6 mg stavudine and 30 mg lamivudine, and *Triomune Junior* is double the baby dose. Current recommendations are suitable for children who weigh six kilograms or more.<sup>23</sup> WHO recommends daily doses of 300-400mg/m<sup>2</sup> nevirapine, 2mg/kg stavudine and 8 mg/kg lamivudine.<sup>24</sup>

*Triomune* for children is available in tablets that are dispersible. They can be dissolved in water to aid adherence and have a bland taste. Many of those unable to procure this formulation are forced to break adult tablets to approximate the dosages.

However, evidence from Zambia suggests that splitting adult tablets can result in low levels of nevirapine, particularly for children with lower body weight for age, or wasting, and in those receiving quarter tablets.<sup>25</sup>

Dr. Kebba Jobarteh notes that "the question is whether this has or does not have an effect on treatment outcomes or adverse effects." "Malawi", he adds, "is currently looking at this question. Split adult formulations are being compared to paediatric formulations to determine whether treatment outcomes with the former are any different from those with the latter."

L'homme and colleagues concluded that if adult tablets must be split *Triomune* 30 is preferable because of the higher nevirapine concentration.<sup>26</sup>

James Nuttal and colleagues, based in the Western Cape, South Africa have compiled a practical drug dosing chart adapted from WHO 2006 and 2008 recommendations to meet the current needs of children infected with HIV or co-infected with TB (see Tools).<sup>27</sup>

Additionally the proposed 2010 WHO dosing guidelines for FDCs

and paediatric dosing of adult formulations can be found in the Tools section.

### Drawbacks to *Triomune*

WHO now recommends the phasing out of stavudine (d4T), a component of *Triomune*, due to its toxicity. Yet the phasing out is not as simple as it may sound. What this means in practice in most resource-poor settings is it leaves only one other option, a zidovudine-based regimen. Aside the logistics and storage problems this presents challenges to care providers in the home as well as the community.<sup>28</sup>

Any alternative to *Triomune* is in pill form but is not dispersible making it very difficult, for children and infants, in particular, to swallow.

Dr. Jobarteh outlined a strategy used to overcome this: "the pills are placed between the surface of two spoons in order to grind the tablet into a fine powder that can then be dispersed in food." He adds, "while far from ideal, it works."

### Previous exposure to nevirapine and low levels of nevirapine-resistant virus – implications for treatment

Nevirapine resistance for those previously exposed to single-dose nevirapine can compromise first-line therapy. WHO recommends that infants and children exposed to nevirapine less than two years previously should receive lopinavir/ritonavir, due to the risk that nevirapine response will be compromised due to the presence of nevirapine resistance.

A heat-stable lopinavir/ritonavir tablet for children, marketed as Aluvia in low and middle-income countries, has been developed by Abbott. Each tablet contains 100mg of lopinavir and 25mg of ritonavir, and will remain heat stable at room temperature for up to six months. This tablet still remains unregistered in many countries, although PEPFAR is exploring with national regulatory authorities ways of expediting access to fixed-dose antiretrovirals for children in advance of registration.

If the heat-stable tablet is not available, lopinavir/ritonavir liquid must be used. Ideally this formulation requires refrigeration but will remain stable at room temperature for six weeks. Unfortunately it has a nasty taste, and there is [a risk of overdose](#) if the dose for body weight is incorrectly calculated.

Other paediatric formulations may also require refrigeration, but intermittent and unreliable energy sources in many resource-poor settings can make this impractical. Dr. Jobarteh highlights "the use of damp sand in clay pots to keep medications between 2-8 degrees Celsius. This is a technique that has been used for ages to keep insulin at the required temperature in resource-limited settings and some patients and families are using this to keep their antiretrovirals cool." Although "far from ideal" he says "it's worth looking into in a more rigorous manner."

In addition long-term metabolic complications make the search for alternative treatment regimens urgent.

### Limited options of antiretroviral medications currently approved and available for children in low-resource settings

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NNRTI	NRTI	Protease Inhibitor	CCR5 Antagonist	Integrase Inhibitor	Fixed dose combination (Triomune Junior and Baby)
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Efavirenz (EFV)***	Abacavir (ABC)*	Lopinavir/ritonavir*LPV/r	n/a	n/a	d4T + 3TC + NVP
Nevirapine (NVP)	Didanosine(ddI)	ritonavir (RTV)**			
	Stavudine (d4T)				
	Lamivudine (3TC)				
	Zidovudine (AZT)				

\*Not widely available in many countries

\*\* limited availability in some countries only

\*\*\* for children over three years of age

## WHO 2010 <sup>30</sup> guidelines recommend

:

For infants under 2 without prior exposure to nevirapine	Nevirapine + 2 nucleoside reverse transcriptase inhibitors (NRTIs)
For infants under 2 with prior exposure	Lopinavir/ritonavir + 2 NRTIs
For infants where exposure is unknown	Nevirapine + 2 NRTIs
For children between 2 and 3 years of age	Nevirapine + 2 NRTIs
For children 3 and up	Nevirapine or efavirenz-containing regimen + 2 NRTIs

- For infants and children the recommended nucleoside analogue backbones are in preferential order lamivudine (3TC) + zidovudine (AZT) or 3TC + abacavir (ABC) or 3TC + stavudine (d4T). AZT is not recommended in cases of anaemia or neutropenia, since it may make these problems worse.

## Taking medicines

Common problems exist among children whether they are HIV-infected or not when they are ill. Children do not like taking medicines, nor do they like swallowing pills. In fact, they are usually unable to swallow them. They need lots of support so the role of caregiver is a crucial consideration when starting treatment in children. Does the caregiver have the time and the skills? Are they psychologically able? Are they dealing with their own and/or others' illnesses too? What is their support network? Is nutrition adequate? Is there a threat to food security?

The bad taste of some medications (for example, the liquid formulation of the protease-inhibitor ritonavir) and the limited choices of treatment regimens available to children infected with HIV make adherence and effective treatment a serious challenge. One practical approach is to give the least pleasant medicine first and ending with the one the child likes most.

Also, children are growing, so dosage must be adjusted in line with that growth to assure the maximum benefits of treatment. Absorption and metabolism of the drugs (pharmacokinetics) will change according to growth and weight. In those under one year of age a monthly adjustment of dosage is needed. Dr. Jobarteh stresses this is only necessary if weight changes significantly enough to warrant such a change.

According to Juliet Houghton of CHIVA-Africa marking syringes to indicate doses helps caregivers who have limited numeracy and literacy skills.

## Adherence

Ensuring good adherence is critical to the success of antiretroviral treatment. In infants and children this cannot be separated from the role of the caregiver(s) noted earlier. Treatment of infants and children must be understood and undertaken within the broader social and economic context requiring a holistic approach.

Problems with adherence as noted include dislike of taking medications, the unpleasant taste of syrups or drugs in powder form, the toxic side-effects, too many pills and difficulties in swallowing as well as the lack of disclosure of HIV diagnosis to the child. Some medications will require food. This assumes that food as well as clean water is readily available.

Not only does the caregiver need to understand and be able to give the medications as required but must be able and willing to attend all appointments. Studies have shown that excellent adherence is possible in infants and children in low- and middle-income countries (attaining better than 75% adherence on average compared to less than 75% in high-income countries). <sup>31</sup>

Mary-Ann Davies and colleagues found excellent adherence in infants and young children in Cape Town, South Africa with the relatively simple low technology measure of adherence by medication return (MR), a strong predictor of viral response. In addition they found, not surprisingly, a better socio-economic status and pleasant-tasting regimens were associated with improved adherence. <sup>32</sup>

A Médecins sans Frontières study in Kigali, Rwanda showed that providing antiretrovirals to children in a health centre/nurse-based programme is both feasible and effective. Key to success included adequate numbers of well-trained nursing staff and a focus on the psychosocial needs of the caregivers and infants and children. <sup>33</sup>

Another study in Malawi supported the need for holistic support strategies that focus on the child, the caregiver and health worker within the context of fragile health systems. Findings suggested that treatment regimens be simplified and cost-free as well as providing culturally appropriate tools to support adherence. <sup>34</sup>

WHO guidelines suggest the use of pill boxes, calendars, diaries or other practical tools to support adherence. <sup>35</sup>

An integral part of the social criteria is 'caring for the caregivers' and says Juliet Houghton of CHIVA-Africa : <sup>36</sup>

- Health needs: including HIV/TB status, mental (psychological) health, own current medications, understanding of own health conditions and adherence to medications
- Financial needs: Including ensuring that all appropriate grants are being obtained and that they have the ability to meet transport costs and clinic appointments
- Social needs: Including who else cares for the child, number of dependents and adults in the household, access to clean water, electricity and sanitation
- Emotional needs: Including whom they obtain support from (including facility support groups if available) and family, friends, faith-based organizations, community-based organizations)
- Learning needs: Including understanding of HIV, ART, side-effects and doses, infection control, food hygiene, storage of ART, preparation of oral rehydration therapy (ORS) and when to return to clinic

- Disclosure of diagnosis: Including level of understanding around diagnosis, ART in the child, along with other family/friends who have been informed.

## Co-infection with tuberculosis - the realities on the ground

Co-infection with tuberculosis also complicates the available treatment options for infants and young children as described in a study by Cordula Reitz and colleagues.<sup>37</sup> This study underscores, as Mark Cotton and colleagues stress in an accompanying editorial commentary “both the lack of antiretroviral options and the lack of adequate data on children who require co-treatment with rifampicin and antiretroviral therapy.”<sup>38</sup>

WHO and the Centers for Disease Control and Prevention (CDC) recommend the use of efavirenz-based regimens for adults who need concurrent treatment with antiretroviral therapy and rifampicin-containing treatment regimens. In children over three years of age the efavirenz + 2 NRTIs is the preferred regimen. Efavirenz, however, is not recommended for use in children under the age of three. WHO recommends for infants and children under three years of age with TB nevirapine + 2 NRTIs or a triple nucleoside regimen.

Cordula Reitz and colleagues report on the virological outcomes of HIV-infected infants and young children (aged 6-104 weeks) treated with a protease-inhibitor based regimen in the Nevirapine Resistance (NEVEREST) antiretroviral study in Johannesburg, South Africa.<sup>39</sup>

40% were co-treated for tuberculosis. The mortality rate was 14%. Almost 100% of those children, not co-treated for tuberculosis, achieved viral suppression compared to 74% who were already receiving TB treatment before starting ART and to 52% of those who started TB treatment after having started ART. For those treated for HIV alone 84% had attained viral suppression less than 400 copies/mL by 39 weeks (nine months of age), comparable to outcomes under ideal circumstances.<sup>40</sup>

In accordance with South African guidelines at that time, all children six years of age or more received lopinavir/ritonavir (250 mg/m<sup>2</sup>), stavudine (1mg/kg) and lamivudine (4mg/kg) every 12 hours. Children under six months of age or those on TB treatment got ritonavir liquid (400-450 mg/m<sup>2</sup>), stavudine (1 mg/kg) and lamivudine (4mg/kg) every 12 hours. Once the children had completed TB treatment or passed the six-year age mark ritonavir was changed to liponavir/ritonavir. All medications were given as syrups and doses were changed at each visit according to body surface area.

The diagnosis of tuberculosis “reflected ‘reality on the ground’ where clinicians initiate treatment on the basis of a constellation of symptoms such as failure to thrive, suggestive radiological findings and contact with a source case,” said Mark Cotton and colleagues.<sup>41</sup> The incidence rate of tuberculosis in South Africa, where for example in the Western Cape the tuberculosis incidence rate is 1596 per 100,000 HIV-infected infants compared to that of 65.9 per 100,000 in HIV-uninfected infants under one year of age supports this ‘method of diagnosis’.<sup>42</sup>

Bacille Calmette Guérin (BCG) immunization (against TB) at birth is a routine procedure in South Africa. Tuberculosis treatment followed South African guidelines: rifampicin and isoniazid for six months with pyrazinamide for the first two months. In cases of BCG disease ethionamide was added to the regimen and treatment was

extended to nine months. Some children with BCG disease also got TB treatment which consisted of rifampicin, isoniazid and ethionamide for nine months.

Dr. Jobarteh notes that there is no conclusive evidence that patients with BCG disease (adenitis) benefit from TB treatment unless it is disseminated. The question here, he continues, is whether ART is enough or not without TB treatment. Citing his experience in Malawi he notes, anecdotally, that TB treatment added no benefit.

So why did those co-treated for tuberculosis have statistically significant worse virological outcomes, and even worse for those who started TB treatment after ART than before, than those treated for HIV alone is?

Mark Cotton and colleagues question whether these outcomes are due to tuberculosis, failure to thrive, breathing problems or radiological abnormalities that suggest treatment for TB, or the inadequacy of the antiretroviral treatment? The answers are not clear cut. While they note that poor adherence might be due to the additional medications for TB, failure to thrive and higher viral load at the start of treatment also contributed to but did not fully explain the differences.

More research is needed on how to use antiretrovirals and TB drugs successfully in children of different ages, in order to determine the correct dosages and understand the factors which lead to poor outcomes in this group of children.

Ritonavir, due to its unpleasant taste has been linked to poor adherence.<sup>43</sup> Ritonavir when used as a single protease inhibitor has also been associated with virological failure and multiple major resistance mutations.<sup>44</sup> Nonetheless ritonavir remains an essential component of treatment of children under three years of age who are co-infected with TB.

The authors note that rifampicin, part of standard treatment for TB as well as BCG disease in South Africa, when given in conjunction with nucleoside reverse transcriptase inhibitors and protease inhibitors produces a drug-drug interaction that may result in sub-therapeutic plasma concentrations in antiretroviral drugs and vice versa.

Cotton and colleagues as well as Reitz and colleagues succinctly note that protease inhibitor based antiretroviral therapy in the “first few weeks of life will reduce mortality and morbidity from HIV-infection and also the risk of acquiring tuberculosis.”<sup>45</sup>

However, they highlight the continuing difficulties of diagnosing tuberculosis in infants and young children. They conclude that the “ideal treatment strategy for young children who require co-treatment with antiretroviral and antituberculosis therapy remains elusive.”

WHO recommendations suggest “starting ART in children with TB and HIV may be delayed if excellent clinical response to TB in the first 2-8 weeks of TB therapy and the child is stable and on co-trimoxazole preventive therapy.”<sup>46</sup>

WHO new guidelines recommend children with HIV who are exposed to TB through household contacts but have no sign of active disease should begin isoniazid preventive therapy (IPT).<sup>47</sup>

## Nutrition

Malnutrition is common in resource-poor settings and is a major cause of death in HIV-infected children.

In an ideal situation WHO recommends that children living with HIV who are asymptomatic get 10% more calories than uninfected children increasing to 20-30% for those recovering from a serious infection or who are symptomatic.<sup>48</sup> Severely malnourished

HIV-infected children should according to WHO be treated following the guidelines for uninfected children and be provided with 50-100% additional calories.<sup>49</sup> Malnutrition should be treated before antiretroviral treatment starts, but this is not always feasible. Treating malnutrition may mean a delay in starting ART.

A daily micronutrient supplement is also recommended where the diet is inadequate or the child appears deficient.<sup>50</sup>

However, ART is recommended in children with sudden weight loss (at clinical disease stage 4), which is not the result of an untreated opportunistic infection and who do not respond to standard nutritional therapy. Conversely a rapid weight gain in HIV-infected children with adequate nutrition and on antiretroviral treatment means dosage needs to be closely monitored and adjusted accordingly.<sup>51</sup>

### Eating difficulties associated with HIV and actions to take

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Oral lesions and thrush will make the mouth sore and swallowing difficult. Once identified, these can be treated with topical medications. Food that is an irritant, such as spicy and acidic foods should be avoided. Cold foods may be better tolerated. A dental assessment as well as good oral hygiene is critical. Rotten teeth are a source of infection and can be the root of severe invasive infection/sepsis if not dealt with.

Poor appetite may improve once treatment begins. Children should be praised and encouraged to eat. Feeding them with a spoon may help; giving small amounts of a child's favourite foods frequently; prescribing a multivitamin supplement and referral to a dietician.

Diarrhoea (see [recent HATIP clinical review](#)) and vomiting may be an early effect of treatment with symptoms improving within one to two weeks or it may be because of a gastro intestinal infection.

- Give frequent small drinks: fruit juice diluted on a one to one basis with clean boiled water, or give oral rehydration salts
- Avoid spicy foods and food with high fat and/or high oil content
- Avoid milk only if it worsens the diarrhoea. Yoghurt may be better tolerated
- Give multivitamin supplement
- WHO recommends giving zinc supplementation as a part of management, according to the guidelines for uninfected children

HIV Enteropathy (chronic, well-established diarrhoea of more than one month's duration and where no HIV-related infectious cause has been identified).

- Usually seen in malnourished children before they start ART or may be due to early side-effects of ART
- Exclude milk protein and lactose from the feed; exclude soya protein if possible
- Specialised formulas containing a hydrolysed milk protein source and glucose instead of lactose are available. For example, in South Africa Alfaré (infants) and Peptamen Junior (children)

Essential components of nutritional support

- Good obstetric care and maternal nutrition to prevent low birth weight and prematurity
- Frequent nutritional monitoring to recognise early growth faltering
- Frequent weight monitoring of HIV positive adults and children to detect weight loss early (possibly suggestive of food insecurity)
- Increased food intake and diversification including periodic supplementation

- Promotion of proper food handling and hygiene
- Prompt treatment of infections that cause weight loss

### ART adverse effects and nutrition

In many cases antiretroviral formulations for children can be combined with food to make it easier to take them. This table sets out the requirements for each as well as the key side-effects of the drug.<sup>53, 54, 55</sup>

Class	Drug	Side Effects	General comments on administration
NRTI	Zidovudine (AZT)	Anaemia, granulocytopenia myopathy, lactic acidosis	No food restrictions and oral solution may be stored at room temperature. Oral solution may be used as an alternative first-line drug to stavudine oral solution for children with body weight under 5 kg and where there is no household refrigerator available. Capsules may be opened and powder contents dispersed in water or mixed with a small amount of food (yoghurt) and immediately ingested. Current available tablets are not scored. Use with caution in children with anaemia due to potential bone marrow suppression.
	Didanosine (ddl)	Pancreatitis, gastrointestinal problems (bloating, flatulence, nausea, diarrhoea, lactic acidosis)	Oral solution requires refrigeration after reconstitution. Discard after 30 days. Capsules may be opened and powder contents dispersed in water (stable in solution for 24 hours) or mixed with small amount of food (yoghurt)
NRTI	Stavudine (d4T)	Hepatic steatosis, lactic acidosis, pancreatitis, body composition changes, peripheral neuropathy	Oral solution requires refrigeration after reconstitution. Discard after 30 days. Capsules may be opened and powder contents dispersed in water (stable in solution



			for 24 hours)or mixed with a small amount of food (e.g. yoghurt).
	Abacavir (ABC)	Hypersensitivity reaction (with or without rash) –may be fatal in adults and children	Caregivers must be warned about potential hypersensitivity which may include fever, rash, gastrointestinal and respiratory symptoms. ABC should be stopped permanently if hypersensitivity reaction occurs. Tablets must not be chewed, divided or crushed; swallow whole with or without food. Once daily dosing is not yet approved for children.
	Lamivudine (3TC)	Diarrhoea, pancreatitis, lactic acidosis	No food restrictions, oral solution may be stored at room temperature. Tablets are scored and can be easily divided; may be crushed and mixed with a small amount of water or food and immediately ingested.
NNRTI	Efavirenz (EFV)	Central nervous system disturbances; gastro intestinal symptoms	Not approved for children under 3. Tablets must NOT be chewed, crushed or divided. Swallow whole, with or without food (banana, yoghurt) Capsules may be opened and powder contents dispersed in water or mixed with a small amount of food (e.g. yoghurt) to disguise peppery taste and immediately ingested. Food, especially high-fat meals, increases absorption. Best given at bedtime to reduce CNS side-effects, especially during first 2 weeks. Consider drug-drug interactions
	Nevirapine	Nausea, vomiting, hepatitis	Once-daily dosing during the first 2 weeks of treatment reduces frequency

			of rash. If a mild rash occurs during the induction period, continue once daily dosing and only escalate dose to twice daily once the rash has subsided and the dose is well tolerated. NVP should be permanently discontinued and not restarted in children who develop severe rash especially if accompanied by fever, blistering or mucosal ulceration. No food restrictions. Tablets can be crushed and mixed with a small amount of water or food and immediately ingested. Avoid NVP if rifampicin is being co-administered. Consider drug-drug interactions
PI	Lopinavir/Ritonavir	Gastro intestinal symptoms; body composition changes	Solution should be taken with food as increases absorption. Solution should be refrigerated however can be stored at room temperature up to 25°C for 6 weeks. May need techniques to increase tolerance & palatability: coat mouth with peanut butter, dull taste buds with ice, follow dose with sweet foods. Tablets must not be chewed, divided or crushed; swallow whole with or without food. Many drug interactions due to RTV inhibition of cytochrome p450.
	Ritonavir	Bad taste, gastro intestinal symptoms, especially diarrhoea, raised liver enzymes, body composition changes	Should be taken with food. May be stored at room temperature, limited shelf life of 6 months. May need to use techniques described for lopinavir/ritonavir to improve

			tolerance of bitter taste
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## Principles for ART in children

These principles<sup>56</sup> assume sufficient and consistent resources including health care workers specialised and confident in paediatric treatment and care.

- Clinical indications may override “normal” CD4 percentage
- Ensure provision of co-trimoxazole, prophylaxis against opportunistic infections including tuberculosis – starting from about 4 weeks of age<sup>57</sup>
- Choose regimens that consider the child’s age and TB status; of note national guidelines usually specify this so there is not a personal health care professional choice involved
- Ensure there is a constant availability of paediatric ART in your facility
- Ensure capacity at facilities to provide ongoing counselling, support and psychosocial assessment and interventions
- Symptomatic monitoring for adverse events
- A holistic assessment and care of the child and family (including psycho social issues, nutritional status and food security, level of understanding and acceptance of ART of caregiver and stage of disclosure to the child) must be undertaken prior to starting ART
- Opportunities for down-referral of child and family to facility closer to home should be sought for implementation once the child is stable on ART.

The challenge to treatment success in resource poor settings also includes adequate numbers of health care workers experienced and confident in the specialized support and care needed for treating infants and children with HIV and their caregivers.<sup>58</sup> And as Dr. Karyn Moshal stresses “In the context of HIV in the developing world [ART for children] is part of routine care where there is high prevalence, it is NOT in any way, shape or form specialized”.

## Conclusion

Dr. Brian Eley, a paediatrician in HIV care since the early 1990s, laments that in spite of the extraordinary progress he has seen “inpatient care of infants with advanced HIV disease in resource-limited settings remains a neglected issue.” “Refining care for these children (under six months of age) requires innovation beyond published knowledge”.<sup>59</sup> he adds in his review of

ound up: building comprehensive HIV/AIDS care in resource-limited setting.<sup>60</sup> Dr. Abrams stated “Alternative approaches and new tools are urgently needed to ensure safe and successful treatment for infants and children with HIV (in resource-poor settings including those co-infected with tuberculosis)”.<sup>61</sup>

## Tools/resources

International Center for AIDS Care and Treatment Programs (ICAP) [www.columbia-icap.org/resources/peds/index.html](http://www.columbia-icap.org/resources/peds/index.html)  
 Book on Paediatric AIDS in Africa, African Network for the Children affected by AIDS (ANECCA) [www.anecca.org/n/HIVAIDS/pub/guide/mans1.htm](http://www.anecca.org/n/HIVAIDS/pub/guide/mans1.htm)

Children and HIV [www.womenchildrenhiv.org](http://www.womenchildrenhiv.org)  
 Africa [www.chiva-africa.org](http://www.chiva-africa.org)

Access strategies within Toolkit published by Baylor International Pediatric AIDS Initiative (BIPAI) [www.bipai.org/toolkit/](http://www.bipai.org/toolkit/)

W. R. G. Teitelbaum SJ, eds. From the ground up: building comprehensive HIV/AIDS care programs in resource-limited settings. Elizabeth Glaser Pediatric AIDS Foundation Publication, 2008. Pp.1935. No charge. ISBN 978-0-9817577-0-4.

[pedaids.org](http://www.pedaids.org)

Guidelines for the use of antiretroviral agents in pediatric HIV [www.AIDSinfo.nih.gov](http://www.AIDSinfo.nih.gov) dosing information is found in the dosing appendix. For updated antiretroviral drug information a prescription can be made to the US Food and Drug Administration HIV/AIDS email list [usfda.hiv.aids@hhs.gov](mailto:usfda.hiv.aids@hhs.gov)

paediatric dosing tools have been developed by the Clinton Foundation HIV/AIDS Initiative (CHA) [www.clintonfoundation.org](http://www.clintonfoundation.org)  
 International Center for AIDS Care and Treatment Programs (ICAP) together with the Baylor International Pediatric

AIDS Initiative(BIPAI)

<http://www.columbia-icap.org/resources/peds/files/dosingguide/pedsdosingguideltrSEC.pdf>

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## Antiretroviral drug dosing charts for children 2009, 2010

compiled by J. Nuttall and S. Raiman for the Paediatric HIV/TB Policy Reference Group, Western Cape. Adapted from World Health Organization guidelines 2006 and 2008. (also in South African guidelines)

	Stavudine (d4T)	Lamivudine (3TC)	Zidovudine (AZT)	Didanosine (ddI)	Abacavir (ABC)	Efavirenz (EFV)	Nevirapine (NVP)
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Target dose	1mg/kg/dose TWICE daily	4-6 mg/kg/dose TWICE daily	240 mg/m <sup>2</sup> /dose TWICE daily	90-120 mg/m <sup>2</sup> /dose TWICE daily	8mg/kg/dose TWICE daily	By wt band ONCE daily	150mg/m <sup>2</sup> /dose *TWICE daily
Available formulations	Sol. 1mg/ml Caps 15,20,30 mg.	Sol. 10mg/ml Tabs 150 mg (scored)	Sol 10mg/ml Caps 100mg Tabs 300mg (not scored)	Tabs 25,50, 100mg (dispersible in 30ml water) Caps 250mg EC	Sol 20mg/ml Tabs 300mg (not scored)	Caps 50 200mg Tabs 50, 200 600 mg (not scored)	Sol. 10mg/ml Tabs 200 mg (scored)
Wt (kg)							
<b>&lt; 3</b> Consult with a clinician experienced in paediatric ARV prescribing for neonates (<28 days of age) and infants weighing <3kg							
3-3.9	6ml	3ml	6ml	avoid	3ml	Dosing <10kg not established	5ml
4-4.9							
5-5.9	7.5mg: open 15mg capsule into 5 ml water give 2.5ml & discard rest			2x25mg tablets			
6-6.9		4ml	9ml		8ml		
7-7.9	10mg: open 20 mg capsule into 5ml water give 2.5ml & discard rest			4ml			
8-8.9							
9-9.9							
10-10.9	15mg: open 15mg capsule into 5ml water	6ml	12ml	1x50mg + 1x25mg tabs am; 2x25mg tabs pm	6ml	200mg cap/tab	10ml
11-11.9				1x50mg+ 1x25mg tabs			
12-13.9							
14-16.9	20mg:open 20mg capsule into 5ml water	½ tab	2 caps am; 1 cap pm	2x50mg tabs am,1x50mg+1x25 mg tabs pm	7ml	200mg cap/tab+50mg cap/tab	1 tab am; ½ tab pm
17-19.9				2x50mg tabs	8ml		
20-24.9	20mg am 30mg pm	1 tab am; ½ tab pm	2 caps	1x100mg tab+ 1x25mg tab twice daily OR 1x250mg EC cap once daily	10ml	200mg cap/tab+2x50mg cap/tabs	
25-29.9	30mg	1 tab	1 tab		1 tab	200mg cap/tab+3x50mg cap/tabs	1 tab
30-34.9				2x200mg cap/tabs			
35-39.9							
>40				600mg tab			

## Antiretroviral Drug Dosing Chart for Children (cont'd)

	Lopinavir/ritonavir (LPV/r) (rtv)	Ritonavir boosting (RTV)	Co-trimoxazole	Multivitamins
Target dose	300/75mg/m <sup>2</sup> /dose LPV/r TWICE daily	**ONLY as booster for LPV/r when on rifampicin TWICE daily	ONCE daily	ONCE daily
Available formulations	Sol. 80/20mg/ml. Tabs 200/50mg 100/25mg	Sol. 80mg/ml	Sol. 40/200mg/5ml Tabs 80/400mg (scored)	Sol Tabs (B Co)
Wt. (kg)	Consult with a clinician experienced in paediatric ARV prescribing for neonates (<28 days of age) and infants weighing <3kg			
<b>&lt; 3</b>			2.5ml	2.5ml
3-3.9	1ml	**1ml		
4-4.9	1.5ml	**1.2ml		
5-5.9			5ml OR ½ tab	
6-6.9				
7-7.9				



8-8.9				
9-9.9				
10-10.9	2ml twice daily OR 100/25mg tabs:	**1.5ml		5ml
11-11.9	2 tabs am, 1 tab pm			
12-13.9				
14-16.9	2.5ml twice daily OR 100/25mg tabs: 2 tabs twice daily	**2ml	10ml OR 1 tab	
17-19.9				
20-24.9	3ml twice daily OR 100/25mg tabs: 3 tabs am, 2 tabs pm	**2.5ml		
25-29.9	3.5ml twice daily OR 200/50mg tabs: 2 tabs am, 1 tab pm	**3ml		
30-34.9	4ml twice daily OR 200/50mg tabs: 2 tabs am, 1 tab pm		2 tabs	1 tab
35-39.9	5ml twice daily OR 200/50mg tabs: 2 tabs twice daily	**4ml		
>40				

\*A lead-in dose of nevirapine is given for the first 14 days of treatment equivalent to half of maintenance dose, that is usual maintenance dose but given once-daily. Increase to full maintenance dose after 14 days if no rash develops.

Body Surface Area (BSA)  $m^2 = \sqrt{\text{Mass (kg)} \times \text{Height (cm)}} / 3600$

WHO proposed simplified table giving number of child-friendly and solid formulations for morning and evening dosing, 2010

Drug	Strength of paediatric tab (mg)	Children 6 weeks of age and above										Strength of adult tab (mg)	Number of tablets by weight band	
		Number of tablets by weight-band morning and evening												
		3-5.9kg		6-9.9 kg		10-13.9kg		14-19.9kg		20-24.9kg				25-34.9kg
am	pm	am	pm	am	pm	am	pm	am	pm	am	pm			
Single drugs														
AZT	60	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300	1	1
ABC	60	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300	1	1
NVP	50	1	1	1.5	1.5	2	2	2.5	2.5	3	3	200	1	1
ddl	25	2*	2*	3	2	3	3	4	3	4	4	25	5	5
Combinations														
AZT/3TC	60/30	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300/150	1	1
AZT/3TC /NVP	60/30/50	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300/150/200	1	1
ABC/AZT /3TC	60/60/30	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300/300/150	1	1
ABC/3TC	60/30	1	1	1.5	1.5	2	2	2.5	2.5	3	3	**		
d4T/3TC	6/30	1	1	1.5	1.5	2	2	2.5	2.5	3	3	30/150	1	1
d4T/3TC /NVP	6/30/50	1	1	1.5	1.5	2	2	2.5	2.5	3	3	30/150/200	1	1
LPV/r** *	100/25	NR		NR		2	1	2	2	2	2	100/25	3	3

WHO proposed simplified table giving number of child-friendly and solid formulations for morning and evening dosing, 2010

\*This dose of ddl is only appropriate for children 3 months of age or older and weighing between 5kg and 5.9kg

\*\*See ABC/3TC FDC dosing table

\*\*\*Higher doses of LPV/r may be required when co-administered with enzyme-inducing drugs such as NVP, EFV, fosamprenavir (FPV), rifampicin.

## Appendix A WHO clinical staging in children

WHO Clinical Stage	Associated Illnesses in Children
1	Asymptomatic Generalised lymphadenopathy – persistent enlarged lymph nodes
2	Hepatosplenomegaly-unexplained enlarged liver and spleen Papular pruritic eruptions- Seborrhoeic dermatitis Extensive wart virus infection Extensive molluscum contagiosum Fungal nail infections Recurrent oral ulcerations Lineal gingival erythema Angular cheilitis Unexplained parotid enlargement Herpes zoster Recurrent or chronic upper respiratory tract infections (otitis media, otorrhoea, sinusitis)
3	Moderate, unexplained malnutrition or wasting: low weight for age, not adequately responding to standard therapy Unexplained persistent diarrhoea (14 days or more) Unexplained persistent fever (above 37.5° C intermittent or constant, for longer than one month) Persistent oral candidiasis (after first 6-8 weeks of life) Oral hairy leukoplakia Acute necrotizing ulcerative gingivitis or periodontitis Lymph node tuberculosis (axillary cervical, inguinal) Pulmonary tuberculosis Severe recurrent presumed bacterial pneumonia Symptomatic lymphoid interstitial pneumonia Chronic HIV-associated lung disease including bronchiectasis Unexplained anaemia (<8gm/dl) and/or neutropenia (<500/mm <sup>3</sup> ) and/or chronic thrombocytopaenia (<50,000/mm <sup>3</sup> ) for < one month)
4	Unexplained severe wasting, stunting or severe malnutrition not responding to standard therapy Pneumocystis pneumonia Recurrent severe bacterial infection (for example, empyema, pyomyositis, bone or joint infection or meningitis but excluding pneumonia) Chronic herpes simplex infection (orolabial or cutaneous for more than one month or visceral at any site) Extrapulmonary tuberculosis Kaposi's sarcoma Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs) Central nervous system toxoplasmosis (after one month of life, that is beyond neonatal period) HIV encephalopathy Cytomegalovirus (CMV) infection: retinitis or CMV infection affecting another organ, with onset after one month of life Extrapulmonary cryptococcosis (including meningitis) Disseminated endemic mycosis (extrapulmonary histoplasmosis, coccidiomycosis) Chronic cryptosporidiosis Chronic isosporiasis Disseminated non-tubercular mycobacterial infection Cerebral or B-cell non-Hodgkin lymphoma Progressive multifocal leukoencephalopathy Symptomatic HIV-associated cardiomyopathy or HIV-associated nephropathy Acquired HIV-associated rectalvaginal fistula (Africa region specific) Penicilliosis (Asia region specific)

## about HATiP

A regular electronic newsletter for health care workers and community-based organisations on HIV treatment in resource-limited settings.

The newsletter is edited by Theo Smart (Cape Town) and Keith Alcorn, NAM's Senior Editor (London).

For further information please visit the HATIP section of [aidsmap.com](http://aidsmap.com)