



# hiv & aids treatment in practice

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## Childhood TB (part 3): treatment and prevention

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### **Palliative care during diagnosis and until a response to treatment**

As the case studies in part two of this series on childhood TB illustrate, a prompt and correct diagnosis followed by curative treatment is the best palliative care for a child with suspected TB. However, the palliative care resources mentioned below offer a number of suggestions on how to approach the child that could reassure the patient and her or his family and help the clinician gather better evidence during the clinic visit (such as finding age-appropriate ways to distract the child, never lying to the child about whether an invasive procedure will hurt and so on).

And especially since the diagnosis of TB (and response to appropriate therapy) can take some time, healthcare workers caring for children with suspected TB should do whatever they can to manage their symptoms and alleviate as much of their suffering as possible. Listing the palliative interventions for the entire spectrum of conditions seen in children with TB would fill a book) so this next section addresses the most common symptoms of TB in children: chronic fever, failure to thrive/weight loss and chronic cough.

### **Palliative care interventions for the most common symptoms of childhood TB**

#### **Chronic fever**

- Give the child cool baths or wipe with damp cloth
- Give plenty of water and other liquids to maintain hydration
- Open windows to allow air to circulate – use a fan if available or fan the child with a book or newspaper
- Give antipyretics
  - Paracetamol 10-15 mg/kg body weight every 4-6 hours
  - Ibuprofen (5–10 mg/kg 6–8 hourly) may also be useful
  - Avoid aspirin in children

#### **Weight loss/failure to thrive**

- Try different foods to see what the child enjoys and will eat
- Feed a little and often, giving high-calorie, high protein food if available, e.g. milk or yoghurt
- Refer to the nutritional supplementation programme or dietician where possible
- Aim at catch-up growth

#### **Cough**

- Positioning for comfort (use extra pillows to raise their chest)
- Humidified air (create steam by heating a pan of water — paying careful attention to avoid hot water burns if using this strategy)
- Keep smoke from cooking fires or cigarettes away from the child
- For children producing sputum, suggest plenty of water and other liquids to loosen secretions
- Suggest cough-soothing remedies such as honey and lemon, steam with eucalyptus leaves or neem tree oil, and/or warm drinks made with honey, cinnamon and ginger
- Provide fresh air (good air circulation is important for good infection control as well)

- Provide support for children taking TB treatment, to make sure that they are taking their tablets regularly and that their caregiver is bringing them into the clinic for follow up

#### Sources:

A Clinical Guide to Supportive and Palliative Care for HIV/AIDS in Sub-Saharan Africa (read online at <http://www.fhssa.org/i4a/pages/Index.cfm?pageID=3361>)

Palliative Care Toolkit: Improving care from the roots up in resource-limited settings (<http://www.helptheospices.org.uk/EasySiteWeb/GatewayLink.aspx?allid=6147>)

IMAI's Palliative Care: symptom management and end-of-life care (see <http://www.who.int/3by5/capacity/palliative/en/>)

#### Pharmacologic treatment of childhood TB

WHO's Pocket Book of Hospital Care for Children recommends giving a full course of TB treatment to all confirmed cases, highly suspected cases — and to children who fail to respond to treatment for other likely diagnoses:

“Treatment failures for other diagnoses include antibiotic treatment for apparent bacterial pneumonia (when the child has pulmonary symptoms), or for possible meningitis (when the child has neurological symptoms), or for intestinal worms or giardiasis (when the child fails to thrive or has diarrhoea or abdominal symptoms).”<sup>1</sup>

Treatment guidelines vary from country to country, but the WHO guidelines suggest three different treatment approaches based upon the [presumed] bacillary load.<sup>2</sup>

1) In the majority of cases of ‘paucibacillary’ childhood TB — smear-negative TB and less severe forms of EPTB (which include tuberculous lymphadenopathy and pleural effusion): *First 2 months (initial phase): isoniazid + rifampicin + pyrazinamide, followed by a continuation phase, either 6 months: isoniazid + ethambutol; or 4 months: isoniazid + rifampicin.*

2) In the case of new smear-positive pulmonary TB or severe disease (including more severe EPTB, except for meningitis and miliary TB) and “severe concomitant HIV disease”: *First 2 months: isoniazid + rifampicin + pyrazinamide + ethambutol (or streptomycin\*), followed by 6 months: isoniazid + ethambutol; or 4 months: isoniazid + rifampicin.*

3) In the case of TB meningitis: *First 2 months: isoniazid + rifampicin + pyrazinamide + ethambutol (or streptomycin\*), followed by 7 months: isoniazid + rifampicin.*

Note: Some experts recommend using this regimen for *any* severe case of disseminated (miliary) disease.<sup>3</sup> In addition, the American Thoracic Society recommends giving the continuation phase for 7 to 10 months.<sup>4</sup> In South Africa, ethionamide is used as the fourth drug since it crosses the blood brain barrier better (see below).<sup>5</sup>

4) Previously treated for TB, smear-positive TB (due to relapse, treatment failure or interruption): *First 2 months: isoniazid + rifampicin + pyrazinamide + ethambutol + streptomycin\* followed by 1 month of: isoniazid + rifampicin + pyrazinamide + ethambutol, followed by another 5 months of isoniazid + rifampicin + ethambutol.*

“This is controversial in children,” according to Dr David Moore, of the Red Cross War Memorial Children's Hospital in Cape Town. “Most paediatricians will actively submit samples for TB culture and susceptibility testing whilst using the same regimen that was used to treat the previous episode of TB.”

This is at least partly because of a justifiable aversion to using streptomycin, unless it is absolutely necessary. Streptomycin should be avoided wherever possible, according to The Pocket Book of Hospital Care, “because the injections are painful, irreversible auditory nerve damage may occur, and there is a risk of spreading HIV due to improper handling of the needle and syringe.”

There are also issues about using several of the TB drugs in children, especially children with HIV. For instance, one medication that was formerly used, thiacetazone, is no longer recommended because it can cause fatal Stevens-Johnson Syndrome reactions in adults and children with HIV.<sup>6</sup>

However, oral ethionamide, which, isn't used in adults because of its toxicity, is better tolerated in children.<sup>7</sup> Marais et al report that dividing the daily dose and slowly increasing up to the full dose over the first couple weeks of therapy helps overcome gastritis and vomiting that may be associated with the drug.<sup>8</sup>

The risk of peripheral neuropathy with isoniazid is greater in children with HIV so the administration of supplemental pyridoxine (5–10 mg/day) is necessary. Dr Moore told HATIP that the actual dose depends upon the formulation of pyridoxine. In South Africa, it may be closer to (6.25–25 mg/day) since the tablets are 25 mgs and scored.

Finally, it should be noted that a higher rate of treatment relapse has been reported on the ethambutol-containing continuation regimen than the rifampicin-containing one in HIV-infected adults. However, the rifampicin-based regimen needs to be provided with directly observed therapy (DOTS) or some other form of good adherence support. Furthermore, there are drug interaction issues between rifampicin and antiretroviral drugs, with rifampicin lowering concentrations of nevirapine, efavirenz and the protease inhibitors (see below).

### **Are the treatment guidelines adequate in children with HIV?**

TB should be treated by state services only, however, many researchers and clinicians have expressed concerns about whether international or local TB regimens are adequate in children with HIV. Several studies have found that outcomes are poorer in children with HIV and TB than in those with TB alone (see Childhood TB, part one).

This might partly be explained by additional morbidity due to other HIV-related conditions in the children. However, a retrospective study by Schaaf et al found that higher than expected rates of relapse and/or recurrence were reported in HIV-infected children on TB treatment in the Western Cape — higher than those observed in HIV-negative children in other studies.<sup>9</sup> Since adherence was reported to be good in these children, the authors concluded that the regimens could be suboptimal.

The TB regimens could be suboptimal in children with HIV in a number of ways. In children with HIV, the immune system may not contribute as much to fighting off the infection, so they may need optimised regimens even when they have smear-negative disease, or the treatment may have to be given for longer. There are also indications that some of the drugs may not be well absorbed in children with HIV (see *Drug dosing* below).

So even though there is little data from controlled clinical trials to support it, many clinicians are adjusting the regimens used in children with HIV.

“In Uganda, based purely on the experience of clinicians, the traditional six months of treatment was increased to nine months for children who are HIV-infected,” wrote Dr Henry Barigye of the Medical Research Council on AIDS (Kampala) in the *Clinical Guide to Supportive and Palliative Care for HIV/AIDS in Sub-Saharan Africa*.

And in another recent paper from Cape Town, Walters et al reported that clinicians who treat HIV-infected children with TB are very wary about using the standard protocols.<sup>10</sup> “Despite local and international guidelines, therapy often has to be individualised. In this cohort, only 75/137 (55%) of TB episodes were treated with the standard 3-drug TB regimen; 33/137 (24%) for the standard 6 months.”

“It does make a lot of sense that if the absorption is lower and your immunity is less, that you've got to increase the doses and you've got to treat for longer,” said Professor Mark Cotton of Tygerberg Hospital, Cape Town, at the 2007 Union World Conference on Lung Health in Cape Town. But there is also a role for ART, he later told HATIP. “ART given during TB treatment will enhance cell-mediated immunity – especially if the child has extensive disease or is severely immunosuppressed — though the danger of drug interactions and IRIS need to be considered.”

## Are suboptimal doses of the TB drugs being given to children?

In fact, several recent publications indicate that children (whether HIV-infected or not) receiving the major TB drugs are exposed to lower serum concentrations of these drugs than adults receiving comparable doses.<sup>11, 12, 13</sup> According to presentations at both the South African TB Conference and later at the 2008 Union World Conference on Lung Health, sixty years since antibiotic treatment for TB was introduced, researchers are only now figuring out how to properly dose the first-line drugs in children (and the situation is even worse when it comes to second line medications for children with drug resistant TB, see below).

“When our current TB drugs were developed, there was little appreciation of the need for higher dosages of drugs in children to achieve concentrations comparable to those of adults,” said Professor Peter Donald of Stellenbosch University, who presented the findings of an exhaustive literature review as well as new data looking at the pharmacokinetics of some of the TB drugs in children at both the South African TB Conference and Union World Conference on Lung Health.

“As children grow, their ability to absorb, metabolise and excrete drugs changes;” he said. “Changes in height and weight are obvious, but what is not so obvious are changes in relative proportions of total body water, extracellular water, body fat and its distribution; protein content, and how the relative size of organs such as the liver and kidneys change.”

And according to Professor Donald children are receiving drug exposures that would be considered suboptimal in adults.<sup>14</sup> (A comprehensive overview of his findings is currently in press).

For instance, WHO currently recommends a 10 mg/kg dose of rifampicin (the same as in adults), but Professor Donald’s research indicates it should be more on the order of 15-20 mg/kg in children weighing less than 10 kg and 10-15 mg/kg for children weighing 10-30 kg.

Children eliminate isoniazid faster than adults, though there are some genetic differences that affect how the drug is cleared (for instance, studies in India report higher drug concentrations in children than seen in other populations).<sup>15</sup> But in most settings, the WHO recommended dose of 5 mg/kg would achieve lower concentrations than seen in adults, according to Professor Donald. Studies in South Africa suggest 10mg/kg would be more appropriate in children.<sup>16</sup> Another benefit of using the higher dose, is that it continues to have activity against most isoniazid-resistant strains (thus, IPT with the higher dose may be useful for children exposed to drug resistant TB (see below).

Similarly, the doses of pyrazinamide should perhaps be higher in children, possibly around 35 mg/kg, rather than the WHO-recommended 25 mg/kg, according to Prof Donald.

Of course, the WHO-recommended doses have been used for years, and in most cases, children respond well to treatment. So are these adjustments really necessary?

“For all current first-line TB agents there is evidence of a dosage-related response,” said Professor Donald. “Of course, many children with TB have really very minimal disease, and the currently recommended doses may work fine for those children, but for more severe forms of childhood TB I believe we need a similar concentration as for adults.”

This may be even more important in children with HIV, but, as of yet, there have been no studies to show whether boosting the doses will achieve better outcomes.<sup>17</sup>

There are also logistical challenges to adjusting the doses of the first-line TB drugs since they come in fixed-dose combinations. At the South African TB Conference, Dr James Nuttall presented the proposed dosing charts to show how existing formulations would have to be given to match the doses that Professor Donald is recommending (a pdf of the adjusted dosing charts can be downloaded by following [this link](#)).

In an evaluation of the dosing chart at the Red Cross Children’s Hospital in Cape Town, Dr Nuttall and colleagues found that the adjustments generally delivered the desired serum concentrations, and only occasionally achieved doses above recommended dose ranges in very young children (who might thus require closer monitoring for toxicity). Notably, the pyrazinamide levels were high in small infants — though,

in that case, the chart uses the same dose, which is already recommended in South Africa for children. However, South Africa still recommends 5 mg/kg dose of isoniazid.

“Breaking up tablets is not the best solution for dosing a child, so improved fixed-dose formulations of TB drugs appropriate for paediatric dosing requirements are urgently needed,” he said. WHO is presently in discussions with pharmaceutical companies about improving the fixed dose formulations of childhood TB drugs, including, notably, ethambutol, which is currently not available in a child-friendly form.

### Drug-resistant TB in children

Professor Simon Schaaf echoed Dr Nuttall’s sentiment when discussing the difficulties of trying to manage children with drug-resistant TB at this year’s Union World Conference on Lung Health in Paris.

As in adults, the WHO recommends that regimens be designed to match the drug sensitivity pattern in the individual or standardised for patterns within the community. And yet, in countries with a very high burden of TB, like sub-Saharan African countries, second-line drugs are mostly not available — especially in formulations that children can use.

“Child-friendly drugs — both formulations and size of tablets or capsules in milligrams — are usually not available. So you split the tablet, but the stability of the drug is also questionable once you have to split tablets and crush tablets,” said Professor Schaaf. “Pharmacokinetic data and knowledge of optimal dose and duration of treatment are mostly lacking in children regarding the second-line drugs. And very little is known about cross-reactions between second-line anti-TB drugs and antiretroviral drugs.”

A couple of other major factors complicate treatment of drug-resistant TB in children. First, second-line drugs are generally more toxic than first-line drugs with some side-effects that are more difficult to monitor in children. Schaaf noted that children tend to tolerate the side-effects of the drug better than adults but that healthcare providers needed to be aware of the side-effects, monitor them closely and attend to them quickly.

### Side effects of second-line TB drugs (from Professor Schaaf’s presentation)

Drug	Side effects	Tests
Amakacin	Ototoxicity	Hearing tests
Kanamycin Capreomycin	Nephrotoxicity	Creatinine, K <sup>+</sup> levels, urine
Ethionamide	Gastrointestinal disturbance	(split dose, escalate)
Hepatotoxicity	ALT	
Hypothyroidism	TSH (T4)	
Fluoroquinolones	Gastrointestinal disturbance Insomnia, arthralgia	Clinical observation
Serine analogues: Cycloserine Terizidone	Psychosis Depression Parasthaesias	More common in adults Less serious with Terizidone Add pyridoxine
PAS	Gastrointestinal disturbance	TSH (T4)
Hypothyroidism		
Linezolid	Myelosuppression Peripheral neuropathy	FBC-HB, platelets, WCC Clinical

	Lactic acidosis	Lactate
	Pancreatitis	Clinical, amylase

Finally, and critically, the diagnosis of drug resistant TB is usually very delayed if it occurs at all.<sup>18</sup> “Children are rarely diagnosed with MDR-TB because cultures are seldom obtained and therefore drug susceptibility testing is infrequent,” he said. (Note, this could change somewhat — at least for smear positive cases — where molecular drug sensitivity tests are being rolled out — provided healthcare workers send specimens from children to the labs).

Dr Schaaf recommended that: “children with known adult MDR-TB source-cases should be treated as MDR-TB until proved otherwise. Because more than 80% of those children will actually themselves have MDR or XDR-TB. And you also need to consider MDR-TB in a child if the child is not responding to or adherent to first-line therapy.”

In general, the management of drug resistant TB needs to become a focus of greater advocacy, because children with drug resistant TB have just as much of a right to effective treatment as adults. It also poses important palliative care and human rights challenges, as the following case study presented by Dr Gary Reubenson at the South African TB Conference illustrates.

### Drug resistance: expert review of case study

*In December 2004, a six-year old boy was admitted to the provincial centre for drug resistant TB, was sputum culture proven MDR-TB. At that stage, the history that was obtained was that his caregiver had recently demised from confirmed MDR-TB.*

*In May 2005, drug sensitivity tests showed he was resistant to five drugs. Two years later in May 2007, TB isolated from his sputum was resistant to six drugs — although not meeting the current definition of current XDR-TB (he was still susceptible to the fluoroquinolones).*

*He's been in the treatment facility for the last four years now, persistently sputum smear-negative and culture-positive. He is HIV-infected but has been on antiretroviral therapy (ART), with an undetectable viral load and a good CD4 cell response for a prolonged period of time.*

The panel of experts felt that the boy had a fairly low chance of being cured with existing TB drugs. Dr Nuttall suggested that surgery might be an option if only an isolated area of his lungs was infected, “But the message here really is that you get one shot at treating MDR-TB and if you don't take that opportunity you'll probably end up with XDR-TB with even less options than you had.”

Dr Reubenson said that unfortunately, the boy's TB was not thought to be amenable to surgery, and that he was currently being given every conceivable drug that might have some anti-TB activity. But without a cure, “What should be done?” he said. “The current treatment guidelines for drug-resistant TB would recommend that after failure to respond after two years, stop TB treatment.”

The clinicians on the panel present said that they would be reluctant to take him off treatment that seems to be keeping him stable. In many cases, Dr Reubenson noted, people taken off treatment progress quite rapidly.

“But to basically commit this child to institutionalisation for a period of two, three or four years on the basis of infection risk is really problematic for a child's quality of life,” said Dr Nuttall, who asked whether he could be sent back to his caretakers and treated on an outpatient basis.

“He's got no one,” replied Dr Reubenson. “No known living relatives, both parents have demised and he really doesn't have anywhere else to go. His TB may well be potentially incurable; he may or may not pose an infection risk to the community. But even if the decision is made for him to be discharged, on or off therapy, he really doesn't have anywhere else to go.”

There are no easy answers. One panellist suggested that perhaps a foster home could be found, but admitted that he wouldn't take the child in because he had two children of his own. In general, the group was

afraid about his being released to an institution because of the risk, even if low, of transmission to other children.

### **ART in children with HIV and TB**

Giving infants with HIV ART dramatically reduces their risk of death, and the same is true in older children with advanced HIV disease. But there is little clinical data to inform when to start ART in children taking TB treatment, or the optimal regimen to use.

“Generally, one initiates anti-TB therapy first in a newly diagnosed patient,” said Prof Cotton. “But depending on how sick the child is, there’s more pressure and urgency to initiate ART earlier — maybe from as early as two to eight weeks [the WHO recommendation<sup>19</sup>] after starting anti-tuberculosis treatment. But in older children you can complete TB treatment first, if they are not severely immunocompromised.”

Recent data, suggesting that outcomes are much better in adults started on ART while on TB treatment, might call this into question (see [this aidsmap news report](#) and [this report](#) also).

But in a child with TB/HIV there are often other palliative and logistical issues to consider. For instance, in the panel discussion at the South African TB Meeting, Dr Francesca Conradie of Helen Joseph Hospital in Johannesburg presented the case of an 8 year old HIV-positive girl who presented with weight loss, cough and night sweats, and then was found to be smear-positive and begun on TB treatment. The panel felt that in most cases, they would probably defer ART.

“I would want to leave ARVs for a while, but then I’m looking at it very much from the social/psychological side of things,” said Beryl Green, a registered nurse who works for the city of Cape Town as a TB/HIV coordinator. “She’s still very young to be supervising her own medication of that level, she’s already having to cope with daily TB medication which is usually quite a number of tablets. Your readiness training in this patient would have to be a lot more intensive than it would in a lot of your adult patients. So I would probably use my TB treatment as almost a practice run for getting that readiness for the ARVs going.”

Dr Conradie agreed: “In a child with a good CD4 count, a good percentage, you wouldn’t consider TB treatment and ARVs until the TB treatment is done. We know the medical stuff, we know when we should, what bloods to take but we forget that this is a little girl. She is only eight years old, I’m not sure if she knows her diagnosis of HIV, she’s certainly at an age when we must be thinking of disclosing to her. And to add to the whole pile, take all these medicines and don’t miss a dose or you will get a drug-resistant virus — is a lot to ask. Clearly when the child is well we have time to work through, not only the medical but also the emotional issues, rather slowly.”

HIV disclosure is less of an issue in younger children (infants and toddlers) and caregivers are usually responsible for ensuring adherence to treatment. If TB was diagnosed in a 3-year-old with HIV, Dr Conradie said she would be more likely to start the child on ART as early as two weeks after starting TB treatment if there was profound immune suppression but otherwise would wait until after TB treatment was finished. However, she said ART should be started as soon as possible in an infant with HIV, regardless of their CD4 percentage.

But the limited options for ART in children can pose a serious challenge, especially in light of rifampicin interactions.

Although it is part of the preferred first-line regimen in adults on TB therapy, efavirenz has not yet been proven safe in children younger than three years of age and less than 10 kilograms in weight and so is not recommended for infants. According to Dr Conradie, it would even be problematic for a three year old.

“Efavirenz only comes in capsules, there’s no efavirenz liquid. So that makes dosing the children something that takes quite a bit of effort. And there are some data to suggest that efavirenz dosing is a bit low — right across the board in children,” she said (see [this aidsmap news report](#)). “Remember in children, the stakes in ARVs are very much higher than in adults. If we decide to start this little girl on ARVs, she’s on ARVs for the rest of her life. And if we lose drugs at this stage, we’ve lost entire regimens that we will never go back to.”

During his talk, Prof Cotton mentioned the same thing: “There’s a very low threshold to getting resistance to non-nucleoside reverse transcriptase inhibitors such as efavirenz. It takes one mutation and you’ve lost that drug. So, if there’s no toxicity, I think one should be increasing the drug level somewhat. And whether it’s 20% or 30%, I couldn’t tell you, but it probably depends on the size of the capsule, which are 50 mgs.”

Another option mentioned in the study Dr Conradie referred to is ‘boosted’ *Kaletra* (lopinavir/ritonavir). The study noted that rifampicin lowered concentrations of *Kaletra* but that this could be overcome by adding more ritonavir (0.75ml additional ritonavir for each 1ml of *Kaletra*) (see [this aidsmap news report](#)).

This was not a popular option in the panel discussion in South Africa. For starters, ritonavir is not available as a single drug to add in many settings. It has other issues as well.

“Has anyone tasted it?” asked Dr Conradie? “It is completely disgusting, absolutely vile! We must remember that we’re giving children medicines and children are different from adults. They spit and throw things up; they knock bottles over. So there are other issues aside from just the straight medication.”

Another approach that was discussed was simply doubling the dose of *Kaletra*. However, a South African study evaluating this approach in children taking with a rifampicin-based anti-tuberculosis regimen recently had to be halted because a high proportion of children had sub-therapeutic lopinavir concentrations.

Another possibility would be a triple nucleoside analogue regimen (such as abacavir/AZT/3TC), though these have shown limited efficacy.

“Finally, in many parts of the developing world nevirapine is really what’s available and in younger children you can’t use efavirenz,” said Dr Nuttall, “so the only option is to increase the dose of nevirapine.”

“We had several cases of children under 18 months who developed TB after starting ARVs, or were very ill and needed to start ARVs before completing TB therapy,” Dr Karilyn Collins, who was Medical Director of Muheza Hospice Care in Tanzania, told HATIP. “On one occasion, we used a 50% increase in nevirapine in a 9 month old when he started on rifampicin. As far as I remember the child survived without any adverse reactions.”

“There are the concerns about co-toxicity, particularly, hepatotoxicity,” said Dr Nuttall, “and efficacy because rifampicin has such a profound affect on reducing nevirapine levels.”

None of these options can be considered reliably safe or effective, and so there is an urgent need for better co-treatment for young children with HIV-associated tuberculosis.

### **TB immune reconstitution inflammatory syndrome (IRIS)**

Finally, there have been reported cases of clinical deterioration in children on TB treatment who start ART (and of undiagnosed TB being ‘unmasked’ in children starting ART).<sup>20, 21</sup> This phenomenon is thought to occur because of ARV-induced restoration of the immune system that reacts vigorously to previously ‘undetected’ TB bacilli in patients who had initiated HAART in the context of profound HIV-related immunosuppression.

The condition is often transient with worsening disease, fever, and increased size of lymph nodes or tuberculomas.<sup>22</sup> But even though cases have been associated with death, it is not clear whether these were directly due to IRIS or other factors.<sup>23</sup> In addition, it is not just ART that can cause IRIS — even improved nutrition or TB treatment have been known to trigger similar events. In light of this, treatment should rarely be discontinued — administering a course of corticosteroids could improve outcomes, however.<sup>24</sup>

### **Strategies to reduce the burden of childhood TB in children with HIV**

Part one of this series of HATIP articles on childhood TB described the increased risk of infection and active disease of HIV-positive children after exposure to TB. Since that time, a paper was published by Hesseling et al in *Clinical Infectious Diseases*, which reported that infants with HIV have a 24.2-fold greater risk of culture-confirmed TB than uninfected infants.<sup>25</sup> They wrote: “Improved tuberculosis control strategies, including maternal tuberculosis screening, contact tracing of tuberculosis-exposed infants coupled with

preventive chemotherapy, and effective vaccine strategies, are needed for infants in settings where HIV infection and tuberculosis are highly endemic.

But the first way to prevent TB would be to go as far upstream as possible — by improving uptake of antenatal HIV testing, improving maternal access to ART, and strengthening prevention of mother-to-child transmission of HIV programmes. This will decrease the number of children born with HIV in the first place. Barring that, diagnosing and providing early treatment of children with HIV should decrease the immunodeficiency that puts children with HIV at greater risk of TB.

“There is a changing scenario for HIV and the South African perspective, and especially the Western Cape perspective: the PMTCT programmes are improving,” said Prof Cotton. “They’ve still got a long way to go but they’re coupled with early diagnosis of HIV in infants which is one of the keys for managing TB.”

In fact, Walters et al reported that putting HIV-positive children on ART led to a substantial reduction in the incidence of TB.<sup>26</sup> The risk of tuberculosis was 53/100 patient years in the nine months previous to ART and 6.4 during follow-up on ART (OR 16.6). “Yet children only accessed HAART at an advanced stage of HIV disease,” wrote Walters et al. “For HIV-infected children living in TB endemic areas, starting HAART at an earlier stage is likely to reduce TB-related morbidity and mortality.”

Another key HIV-related intervention, cotrimoxazole prophylaxis, improves survival in HIV-infected children and reduces the incidence of respiratory infections and related hospitalisation.<sup>27</sup> It might also reduce the burden of TB in children with HIV, since active TB disease often happens in the context of other respiratory infections, and since children who are hospitalised for such infection may be at a greater risk of nosocomial transmission of TB. Finally, it has also been shown to improve outcomes of adults with HIV and tuberculosis.<sup>28</sup>

### **Contact tracing and intensified case finding**

In a recent study, Professor Schaaf and colleagues reported that around 64.3% of children under 5 with confirmed TB were household contacts of adults who had been previously diagnosed with pulmonary TB. These represent missed opportunities for prevention.<sup>29</sup>

“Identifying and treating TB infection and disease in children can provide long term benefits to TB control and prevent future cases due to reactivation,” said Dr Rangsimha Lolekha of the US Centers for Disease Control office in Thailand, speaking in a session on contact tracing at this year’s Union World Conference on Lung Health. “But even though WHO recommends TB disease screening in children who live in a household with a smear-positive case, few national TB programmes perform these routinely.”

Indeed, the NTP Guidance recommended “that all National Tuberculosis Programmes (NTPs) screen household contacts for symptoms of disease, and offer isoniazid preventive therapy (IPT) to children aged <5 years and to all human immunodeficiency virus (HIV)-infected children who are household contacts.”<sup>30</sup> But it also noted that it “rarely happens in low-resource settings, where the majority of childhood TB occurs.”

Most countries have a ‘policy’ on contact tracing but it is rarely translated into guidelines that are available at the local level. Dr Lolekha and colleagues sent out a questionnaire to TB care providers throughout Thailand. 65% said that contact screening was policy, but only 26% of those said that it existed as a written policy. 85% of the respondents said that contact tracing was under-utilized; and most said it was because it was not a programming priority or policy, and because they were too short staffed.

Another recent study in Malawi reported: “In practice, screening of child contacts rarely happens, despite its being recommended by the Malawi NTP. Many health workers in Malawi are not aware of the rationale for contact screening. There are many resource constraints within the NTP, resulting in priority being given to effective management of the most infectious cases.”<sup>31</sup>

Furthermore, studies in Britain, India and Kenya have previously reported that the yield of contact tracing was low and not worth the time or expenditure.<sup>32, 33, 34</sup> However, more recent contact tracing studies from South Africa have found that as many as 34% of the household contacts under the age of 5 were diseased, and another 14% infected.<sup>35</sup>

The success of the intervention may depend on how and where it occurs. For instance, in a study in Malawi, people with smear-positive TB were asked to bring their children into a centralised clinic for screening, but only 7.7% did so.<sup>36</sup> “This is costly and impractical for many families, and it is particularly difficult to convince them of the benefit when the child is well,” wrote the study’s authors, who suggested more decentralised screening.

Community based intensified case finding could be more effective than waiting for people with TB to bring in family members. Furthermore, HIV programmes and community based organisations could share a role to follow-up on contact tracing of their clients who are diagnosed with HIV in the context of general family-based interventions such as HIV screening and providing a basic package of care. Childhood contacts who are identified can be assessed with a simple symptom screens if necessary (see [HATIP # 104](#) on intensified TB case finding). Antenatal and PMTCT programmes should also consider screening pregnant women for TB because the risk of the child getting infected during or after delivery is much less if the mother has been on treatment for a few weeks.<sup>37</sup>

### Preventive therapy

Contact tracing must be linked to preventive therapy for any child with HIV who has had significant contact with a person with TB (particularly household contacts). There are essentially two preventive therapy regimens, isoniazid preventive therapy (IPT) (six months, nine months or continuous) and combination isoniazid/rifampicin (or rifapentine) preventive therapy (for three months). Currently, six to nine months of IPT is the most widely recommended and used preventive regimen.

The WHO recommends the provision of IPT to all household TB contacts aged below 5 years, and this is policy in most countries, but as [HATIP #96](#) described, it is not being routinely implemented. That issue of HATIP reported the abundant data in support of the use of IPT in adults with HIV.

A prospective double-blind placebo-controlled clinical trial has also shown that IPT reduces the risk of TB in children with HIV in a setting with a high burden of TB. The study included 263 HIV-infected children aged 8 weeks or older (median 25 months) with advanced HIV disease.<sup>38</sup> They were given cotrimoxazole in combination with either IPT (at the 10 mg/kg dose) or placebo. IPT was intended to be given continuously for two years, however the median follow-up of the study was only 5.7 months, at which point the study was stopped because of a strong reduction in mortality (50%) in the IPT arm. IPT also reduced the incidence of TB by 70% though this did not explain the difference in mortality.

A more recent IPT study, PACTG 1041 was also discontinued when it was clear that it wouldn’t be able to reproduce similar results in a much larger cohort of HIV-exposed children, (aged 3 to 4 months at enrolment.).<sup>39</sup> Notably, the study included a majority of HIV-negative children who would not have had the same risk of developing active disease. However, a preliminary subset analysis of the HIV-infected children in the study found no benefit over placebo in this group either, with roughly 8-10% developing TB in each arm. This rate seems somewhat high, so one has to wonder whether there was good adherence to IPT.

There were a couple of other differences between the two studies. Many of the infants with HIV also went on ART, which would make the children with HIV less likely to progress to TB than in the earlier trial. But in addition, children had very frequent contact with the clinic and were put on IPT if they were found to have a new TB contact —so, in a sense, this was a study of deferred IPT versus immediate IPT. The time that TB-exposed infants actually went without IPT was very short. Such intensive TB screening may not currently be the routine experience of most children in a programmatic setting however — but, Dr Cotton told HATIP, it easily could be.

“Infants with HIV should be brought into clinic frequently, for ART and cotrimoxazole refills. Similarly HIV-exposed children have to come in frequently for monitoring and so on. So routine frequent assessments of TB contact are quite possible,” he said.

The data continue to support providing preventive therapy to young children who have been exposed to TB — though there is a clear need to make certain that adherence is improved.

Adherence might be somewhat better on the isoniazid/rifampicin or rifapentine combination regimens because they are of shorter duration. A meta-analysis suggests that isoniazid/rifampicin is of equal effectiveness to IPT in adults (see [this aidsmap news story](#)).<sup>40</sup> In addition, at the Union World Lung Conference this year, Martinson et al reported that isoniazid in combination with either rifampicin or rifapentine were equally effective to isoniazid ((given either for 6 months or continuously) (see [this aidsmap news story](#)). Although there aren't any data in children with HIV yet, a study in HIV negative children with latent TB in Greece found that there seemed to be more chest x-ray evidence of TB in children taking 9 months of isoniazid than in those taking three to four months rifampicin/isoniazid.<sup>41</sup>

In high TB burden settings (such as the townships in the Western Cape), it may make sense to use a shorter course regimen to older HIV-negative children who are TB infected before they begin to become sexually active (and potentially HIV-infected) — as this could reduce the burden of TB in the next generation of young adults and parents.

But younger children with HIV are at an ongoing risk of exposure to TB — and the protective effect of a shorter regimen only lasts as long as it is being taken. It cannot prevent new infections that may occur subsequently. In fact, in a Kaplan Meier analysis in the study by Martinson et al, the continuous isoniazid arm clearly looked more effective in the first couple of years on treatment, but after a few years the benefit was lost as participants stopped taking it.

But in a context where children with HIV are at a high risk of ongoing exposure and of rapidly progressing to disease, a continuous regimen might provide more continuous protection. In addition, rifampicin/isoniazid requires intensive adherence support (or directly observed therapy), since poor adherence could lead to resistance to the most important drug in the TB regimen.

But perhaps the greatest concern regarding rifampicin/isoniazid is the risk of drug interactions for any child who may be on, or need to start ART while still taking rifampicin.

### **IPT - a case study**

Back at the skills building session at the South African TB Conference, Dr Gary Reubenson asked the panel what they would do when a baby is born to a mother with TB.

“You should look at the [drug] sensitivity of the mother; and obviously you need to do a TST, do a clinical and laboratory investigation of the child to rule out active disease,” said Dr Mo Archary. “You do not give BCG (vaccine) at that visit. If you've ruled out active TB, the child should go on to six months of INH (isoniazid) prophylaxis and then you retest the child at three months with a repeat chest x-ray and a Mantoux and re-evaluate the lab results. Then you decide whether the child goes onto full TB treatment or comes off INH prophylaxis.”

“The issue here is deciding whether the child has active TB or not, and if the child does not have active TB, the crux of it is careful follow-up of the child, and to make sure that you monitor growth, you monitor respiratory symptoms and other symptoms of active disease,” he said.

“This child will definitely end up on prophylaxis in our service,” said Beryl Green, but she had concerns about getting the dosage of isoniazid right for a small child since only 100 mg tablets are available, and these are difficult to break into eighths (to dose 5 mg/kg).

However, Dr Nuttall said that there was increasing recognition that higher doses of INH are warranted in younger children. “You can break [the isoniazid tablet] into a quarter which will be 25 mgs. For a 2 kg baby, that would be roughly 12.5 mg/kg which is within the range of the [proposed dosing chart]. It may not be absolutely accurate like [measuring out] a syrup that you can calculate exactly the dose, but it's an approximation and it's safe,” he said.

But for the time being, the currently recommended dose is lower, so “in light of the dosing challenges, very often these children end up on three-month, two-drug prophylaxis, rifampicin and INH,” said Green. “What we would use in the continuation phase for a child with active TB, we just use for three months prophylaxis in these tiny ones.”

“A two-drug regimen for three months may have a better adherence than six months of isoniazid alone,” said Dr Nuttall. “But there are other implications of starting a child on rifampicin. It’s really a core drug in the treatment regimen and so the recommendation is that if you’re going to use two drugs, it should be under directly observed therapy. So it’s very similar to putting a child onto TB treatment, they should be attending a clinic setting where they can have that directly observed for three months.”

“The other issue is that with the move to put all HIV-infected infants onto antiretrovirals very early, the implication is that if there are children who then are put onto rifampicin/INH prophylaxis, that’s going to influence the regimen and *Kaletra* will require boosting and may make overall adherence more difficult. If they are on antiretrovirals, they will be under fairly close follow-up in terms of the antiretrovirals. So theoretically, INH may be better; they may be more adherent to INH because they’re in a sort of ARV adherent system hopefully. On balance, probably, I’d go with the INH.”

Another issue mentioned by Dr Archary, was that when TB preventive therapy is given from birth, the BCG vaccine will need to be deferred until either prophylaxis or treatment has finished in this child.

Dr Nuttall agreed, “obviously if you give somebody BCG (a live vaccine) and they take INH a few hours later, you are effectively killing the BCG, killing the organism. And therefore it’s not really going to be effective in eliciting and in generating an immune response,” he said.

But there are other concerns about BCG vaccination in children with HIV.

### **BCG: To vaccinate or not to vaccinate?**

Bacillus Calmette-Guérin (BCG) is a vaccine derived from a weakened strain of the live bovine tuberculosis bacillus, *Mycobacterium bovis*. It is given routinely to infants in settings where TB is endemic. Although data suggest that it has mixed success at preventing TB, it does appear to prevent the more serious forms of disease (such as miliary TB and TB meningitis) in HIV-negative children.<sup>42</sup>

In children with HIV however, it is not clear that it offers much benefit<sup>43</sup> and, in fact, BCG has been associated with the development of disseminated BCG infections that can be life-threatening (see this [aidsmap news story](#)).<sup>44, 45</sup> In fact, the incidence of BCG disease has been reported to be as high as 407-1300 per 100,000 infants in HIV-infected children who have been given the vaccine in South Africa and Argentina, with a mortality rate of more than 75%.<sup>46, 47, 48</sup>

Since the benefits of BCG seem to be outweighed by its risks, the WHO changed its recommendation regarding the BCG vaccine for children known or suspected to be HIV infected.<sup>49</sup> But at the same time, denying or delaying BCG might pose a risk of severe TB to uninfected children in high TB burden settings. When making their decision about how to move forward, WHO suggested that local programmes consider the local burden of HIV and TB, the risk of TB exposure for the child, the strengths of the PMTCT programme, feeding practices, child health, the ability of immunisation programmes to follow-up on children, and the ability to get an early diagnosis of HIV in children (by HIV DNA or RNA PCR, or p24 antigen tests).

But the guidance acknowledged that the same countries that have a high burden of HIV usually have a high burden of TB, so the children of women with unknown (or HIV-negative) status should still all be vaccinated at birth. If, however, the mother was known to be HIV-positive, the policy may depend on the factors already mentioned. If the child’s HIV status is unknown but there are no symptoms of HIV, then the guidelines suggest the child should be vaccinated. If the child is known to be HIV-infected, vaccination is contra-indicated. If the child’s status is unknown, but there are symptoms suggestive of HIV, the child should not be vaccinated, at least until their HIV status could be determined.

However, there have been several problems implementing this new policy.<sup>50</sup> First and foremost, when BCG vaccination occurs — in the wards, generally very soon after birth — the child’s HIV status is almost always unknown. Could setting up a two-tiered system in the MOU unit really work — making spot determinations about whether to defer vaccination in an HIV-exposed child? There would be a number of operational challenges putting such a system in place.

During the panel discussion at the South African TB Conference, opinions were mixed about what would be the best way forward — with some panellists preferring to defer BCG for all HIV-exposed children until PCR

results become available. Others thought that would be unworkable. “We would lose a lot of the babies because of their unknown status,” said Dr Archary.

According to a recently published consensus statement from the BCG Working Group, Child Lung Health Section, of the International Union Against Tuberculosis and Lung Disease, “A key implementation consideration is the ability of infant vaccination and PMTCT programmes to allow for strategies such as selectively delaying vaccination of HIV-exposed infants from birth until, for example, 10–14 weeks of age, following a negative HIV PCR testing result, e.g., at 4–6 weeks of age. This could be combined with alternative TB preventive strategies such as isoniazid preventive therapy in the intervening period. Such strategies will have to be implemented in close collaboration with other infant health programmes and will require fully functioning and integrated PMTCT and infant vaccination programmes with appropriate follow-up.”<sup>51</sup>

The consensus statement goes on to say that these conditions simply don’t exist in most settings with high burdens of HIV and TB, so implementation of selective vaccination strategies just isn’t feasible right now for most programmes. Until such a day as it is feasible, “universal BCG immunisation of infants [should] continue in countries highly endemic for TB until countries have all programmes in place for implementing selective deferral of HIV-exposed infants.”

Ironically, countries that implement strong PMTCT with good TB screening in mothers will have less need for a selective immunisation policy. Furthermore, if countries implement early HIV testing of children, and quickly put those who are HIV-infected on ART, there should be a lower risk of BCG disease developing. However, there have been reports of BCG IRIS in vaccinated children put on ART.<sup>52, 53</sup>

Clearly a better option is needed.

In the paper just published by Hesselting et al, the authors wrote, “improved tuberculosis vaccine strategies are required. New vaccine candidates should be tested among HIV-infected and HIV-exposed infants in settings where tuberculosis and HIV infection are highly endemic.”<sup>54</sup>

### **Research agenda**

Indeed, as we hope this series of articles demonstrates, research is needed on virtually every front of diagnosing and managing childhood tuberculosis. It’s time to end the neglect.

In a recent editorial calling for children to be involved in the trials of new TB drugs in development, Burman et al wrote, “Children have the same right to benefit from research as do adults.”<sup>55</sup>

A forthcoming HATIP in 2009 will address the state of TB research, and among other things, will review the key areas for research in children — and how the HIV and TB research establishments can try to address them.

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