

HATiP

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In this issue:

Combining ARVs with treatment for tuberculosis; *page 2*

- Abbreviations used in this article
- The Global Challenge
- Impact of ARVs on TB
- DOTS is essential (but not currently sufficient)
- The need for active case finding
- An outline of TB treatment
- Secondary prophylaxis with isoniazid
- Combining TB treatment and ARVs
- Interactions between ARVs and anti-tuberculous therapy
- Efavirenz and rifampicin
- Nevirapine and rifampicin
- Saquinavir/ritonavir and rifampicin
- Abacavir and rifampicin
- Working treatment out in practice
- Paediatric treatment
- Integrating TB and HIV treatment services
- Further information on aidsmap
- Other Internet resources

Combining ARVs with treatment for tuberculosis

By Julian Meldrum, with many thanks to advisory panel members including, in particular, Anton Pozniak, Desmond Martin, Harry Hausler, Henry Barigye, Leon Regensberg and Vijay Anthony Prabhu. This article also refers to a presentation by Dr Richard Chaisson at the 2003 Conference on Retroviruses and Opportunistic Infections, held in Boston, USA - for which webcast details are given at the end.

Abbreviations used in this article

3TC = lamivudine

ARV = antiretroviral drug

AZT = zidovudine

d4T = stavudine

EFV = efavirenz

NNRTI = non-nucleoside reverse transcriptase inhibitor (e.g. NVP, EFV)

NRTI = nucleoside analogue reverse transcriptase inhibitor (e.g. AZT)

NVP = nevirapine

The Global Challenge

As Dr Richard Chaisson explained in Boston, tuberculosis (TB) is the commonest HIV-related disease in many countries. At a global level, the interaction between HIV and TB is clearly the greatest public health challenge posed by the HIV epidemic.

- People with HIV progress more rapidly than others from latent TB to active TB, with the potential to infect others regardless of their HIV status.
- People with HIV who are exposed to TB are more likely than others to become ill with primary active TB. If they are exposed to multi-drug resistant TB, many die before completing a first course of treatment.

The impact of TB on the progression of HIV disease is also important.

Impact of ARVs on TB

Treating HIV with ARVs reduces the risk of TB by as much as 80%, but the risk of TB is already high by the time CD4 counts are low enough to require ARV treatment (200 cells per cubic mm).

- In Brazil, a TB incidence of 8.4% p.a. was reduced by 80% with HAART. Similarly, Baadri and colleagues in Cape Town showed that in a group of patients with CD4 counts below 200, TB incidence was reduced from 17% to 3% p.a. (but this risk is still very substantial indeed).
- ARV access on its own has not prevented a rise in TB cases among people with HIV. In Northern Thailand, TB cases among people with HIV have continued to rise despite reductions in HIV incidence.

MARTIN: As most current guidelines specify treatment when the CD4+ count falls below 200 we miss preventing a considerable number of TB cases that occur in the CD4+ stratum between 200 - 350. Perhaps these cases could be prevented by the institution of isoniazid chemoprophylaxis when the CD4+ count falls below 350 [regardless of TB exposure status]. Research has shown however,

that a positive benefit occurs in a group of individuals who were tuberculin skin test positive.

Our experience has been that there is an increased progression of HIV disease in the presence of TB. Previous research work that I was associated with had revealed an intense immune activation associated with TB in the HIV-infected individual and this was manifest with high viral loads, markers associated with immune activation (CD38, HLA-DR markers being increased). The high viral loads often remain even after successful microbiological cure of the patient.

DOTS is essential (but not currently sufficient)

The WHO's DOTS [Directly Observed Treatment, Short-course] strategy - while still a valid approach to treatment - is clearly not sufficient. In Southern Africa, efficient TB programmes following WHO guidelines and meeting WHO targets have not been able to prevent a rising tide of cases.

- In Botswana, a well-managed DOTS programme has achieved 90% completion rates for treatment, yet TB remains the leading cause of death among people with HIV.
- In South African gold miners, with routine active case finding and extremely efficient DOTS programmes, there has been a similar failure to reverse an increasing TB incidence.

One possible conclusion is that treatment should extend beyond active TB to identify and treat latent TB, and some HIV treatment services are now doing this. A future issue of HATIP will discuss this approach, which remains controversial. However, there can be no doubt at all that people with HIV who have active TB must be treated for their TB.

In Rio de Janeiro, expanding DOTS (vs self-administered therapy) among people with HIV who had active TB substantially increased treatment completion rates and reduced death rates. This benefit was additional to the benefit obtained from providing ARV treatment to this population.

In other countries, such as Russia and India, there is still a long way to go before there are effective DOTS programmes.

PRABHU: India bears a large burden of the global TB incidence. Private practitioners see a large majority of TB patients initially and the discrepancy in management practices is worrying. Private GPs see themselves, at times, alienated from national programmes, with no specific role for them. In India, a revised national TB control programme is being implemented based on DOTS methodology. We need to encourage private- public partnerships in the implementation and expansion of DOTS, but this seems to be at present an unfulfilled dream. The State insists on control and the private GP would not like to lose his or her patients. DOTS is lost somewhere in between.

An NGO setup can only do so much for the patient. NGOs may not have sputum microscopy and radiographs available, in which case the NGO doctor/health care worker must decide what to do next. If he refers to the state government sector, then more often than not, the reception the patient gets is not pleasant. The patient is treated as an unnecessary burden on their already stretched resources. The state wonders: why can't the NGO pay for the tests? A sea of suspicion exists between private and public sectors! The patients are made to wait in endless queues. Tests are performed after much delay, it is sometimes a wonder that the patients go through it all and come out in one piece alive and healthy. In the era of email and computers, communication is sorely lacking. The results of the tests are on small snippets of paper, the much wanted radiographs may be of poor quality or filed away in the department records. The

patient is informed that he has TB and started on anti-tuberculous therapy (ATT). What starts as a referral for a couple of investigations, ends up with initiation of therapy which may be unwarranted, with no communication to the referring physician. The control then shifts to the public sector and the private sector may get to see their patient after a couple of months... the patients, not the public doctors, inform their NGO physicians that they were started on ATT, they felt better or are feeling worse and so now have stopped and come back. It is thus essential for effective communication and partnerships to be forged between private and public sectors, to see what each can contribute and to work out their differences.

The need for active case finding

The DOTS strategy rests mainly on rapid identification and proper treatment of active pulmonary TB. Ensuring that sputum samples are taken from anyone who has a persistent cough continues to be essential to prevent onward transmission. However, people with HIV are more likely to suffer TB outside the lung than people without HIV. Diagnosing and treating these other forms of TB is a vital part of healthcare for people living with HIV. TB diagnosis can therefore be enhanced by routinely screening HIV-positive clients for TB symptoms at every visit

At Chris Hani Bharagwanath Hospital, Soweto, HIV positive mothers were offered tuberculin skin tests - half of them were positive and 3% had active TB that had not been diagnosed.

In Cambodia, routine sputum collection on monthly home visits to people diagnosed with HIV revealed that 8% were sputum positive and half of these were confirmed, previously unsuspected cases of TB.

HAUSLER: In 1999, the South African Department of Health established four TB/HIV Pilot Districts that implemented and evaluated a comprehensive package of TB/HIV/STI prevention, care and support. The package included strengthening TB/HIV public/private collaboration, voluntary counselling and rapid HIV testing, active TB case finding among HIV-positives, isoniazid TB preventive therapy for HIV-positives with no TB symptoms, co-trimoxazole prophylaxis and better management of opportunistic infections. People living with HIV were screened for TB symptoms at baseline and symptomatics were investigated for TB. The proportion found to have active TB as a result of active case finding was 3% in Bohlabela (Limpopo), 7.4% and 9.8% in East London (Eastern Cape). Active case finding therefore detects a large number of TB cases which allows earlier initiation of TB treatment and decreases TB transmission.

MARTIN: It is absolutely essential that no opportunity be lost to diagnose TB. A high index of suspicion is necessary and any persistent cough must be vigorously investigated. In addition TB contacts and inmates of prisons, hostels, crowded slums should be under active surveillance.

Early diagnosis is important and as it is our commonest OI this should be aggressively pursued especially in the case of smear negative disease. Blood and bone marrow examinations should be carried out and fine needle aspirates of lymph nodes should be performed. There are many practitioners in our region who carry out a trial of therapy when they have been unable to establish a diagnosis. This is particularly done when there are abnormal syndromes associated with a smear negative picture. I still feel aggressive pursuit of a diagnosis is a better pathway.

PRABHU: Since HIV patients are prone to respiratory infections, questions and physical examination need to be thorough. A good clinical history and proper physical examination have no substitutes.

They provide an invaluable insight into the patients body and guide clinical and lab investigations. Sometimes they are all we have at our resources, since the patients may be extremely poor and unable to afford even a basic sputum test and radiographs.

The most important point is to approach with an open mind. We must not think of TB even before we put our stethoscopes on, in which case, anything the patient says or we find, will fit in with TB. It may well be a deadly trap which we can get our patients into. Bacterial pneumonias of varying etiology are exceedingly common, and treatment must be based on local epidemiological data. An empirical trial of a good powerful antibiotic is given and the clinical response judged. If the patient feels better, then good. If not, we are both in trouble. What organisms are we dealing with, are they resistant, how do we further work up the case keeping in mind the financial constraints?

Detection of extrapulmonary TB is challenging, since in these instances routine sputum microscopy is negative. The expenses incurred in the diagnosis burn a huge hole in the patients pockets -special investigations need to be ordered, biopsies have to be done to get a tissue diagnosis. The patience and resilience of the physicians are tested. Patients have to be cajoled into undergoing these tests, which may still come back as negative - in which case, the patient wonders why he went through it all. Radiology, pathology, microbiology and surgical departments have to work together to perform a battery of tests in order to detect and diagnose extrapulmonary TB. It is very much the physician's prerogative to investigate, the more he probes the more he may uncover and herein lies the difficulty... how much is enough? There are no guidelines in the diagnosis of extrapulmonary TB... individuals vary in the thoroughness of their investigations and accordingly case detection rates vary.

An outline of TB treatment

Protocols for treating TB are established nationally and should be followed for people with HIV in the same way as for people without HIV. This outline is set out purely as a background to the discussion of ARV treatment which follows.

Initial treatment for tuberculosis under DOTS programmes is standardised in most countries. It is usual to begin with a four-drug regimen for two months, followed by a two-drug maintenance regimen: four months of rifampicin and isoniazid or six months of ethambutol and isoniazid.

The four-drug regimen normally begins with daily rifampicin, isoniazid, pyrazinamide and ethambutol. This may be replaced after two weeks with twice-weekly dosage of the drugs, although treatment patterns vary from country to country.

Isoniazid may be supported with pyridoxine (vitamin B6) to prevent peripheral neuropathy.

MARTIN: In the case of extrapulmonary TB many practitioners give a further 3 months of 2 drug therapy.

Secondary prophylaxis with isoniazid

TB treatment is equally effective regardless of HIV status, although people with HIV are at much higher risk of re-infection and recurrence after being cured. There have therefore been trials of secondary prophylaxis using isoniazid.

In Haiti, according to Chaisson, isoniazid treatment following TB cure was shown to reduce the relapse rate among people with HIV.

In South Africa, secondary prophylaxis with isoniazid is not currently offered in the public health system.

Combining TB treatment and ARVs

There are four main concerns about combining TB treatment with ARVs.

1. When to start WHO recommends the following for HIV-positive TB patients:

- CD4<50: start ARVs as soon as TB therapy tolerated
- CD4 50-200: start ARVs after 2 months of TB therapy
- CD4>200: monitor CD4 and start TB therapy if CD4 drops below 200.

Obviously, this depends on the availability of CD4 counting!

2. Pill burden: TB treatment involves taking many tablets as do most ARV regimens. Higher pill burden often results in lower adherence. For this reason it is better to delay ARV treatment until the intensive phase of TB treatment is completed.

3. Immune reconstitution inflammatory syndrome (IRIS). There can be a transient worsening of clinical status of TB patients 2-3 weeks after initiation of ARVs. Sometimes, this occurs in patients who have not previously been diagnosed with TB, who may even have been negative on a Mantoux test. The syndrome is characterised by fevers, lymphadenopathy and worsening pulmonary lesions that are caused by increased inflammatory responses from a strengthened immune system. These reactions are typically self-limiting but may require a course of corticosteroids to reduce the inflammatory response.

4. Interactions with rifampicin and drug toxicities: discussed below.

POZNIAK: As far as IRIS is concerned the Spanish and Italians try to avoid it by delaying HAART for at least 2 months, even in patients with a low CD4, as it is believed IRIS is commoner in these patients but there are few data to support this. We have data to show that the problem with delaying ARV treatment is that you run a risk of AIDS or death. If IRIS happens, treat with steroids if symptomatic and for as long as you need to, sometimes for months. Note that the dose of steroids may have to be increased as rifampicin induces steroid metabolism. Aspirate tense lymph nodes especially if the surrounding skin is red - exclude other OIs, though. In extreme cases, consider stopping ARVs.

Interactions between ARVs and anti-tuberculous therapy

This section draws on the excellent guidelines produced by the Southern African HIV Clinicians Society.

There are two main problems with combining TB treatment and ARVs.

The first is that the anti-TB drug rifampicin is a potent inducer of the liver enzymes which the body uses to break down several anti-HIV drugs, including protease inhibitors, the non-nucleoside reverse transcriptase inhibitor delavirdine and (to a lesser extent) nevirapine and efavirenz. The outcome is reduced levels of the ARV drugs in the body, which may lead to the development of HIV drug resistance.

The second is that when patients are treated with more than seven active drugs (remembering that guidelines also support co-trimoxazole prophylaxis for people with HIV and active TB, as discussed in HATIP #1), the likelihood of side effects is high. When side effect profiles overlap, working out which drug is responsible may be difficult. Caution should be used when combining isoniazid with d4T, ddI or 3TC which can all induce peripheral neuropathy.

If a patient is newly diagnosed with HIV and active TB, the simplest way to manage these problems is to begin by treating the TB and delay ARV treatment until the four-drug phase of TB treatment has been completed.

However, if the patient has a low CD4 count, has suffered from previous HIV-related illnesses, and is clearly at high risk of progression, there may be a need to commence both at the same time.

Also, if a patient who is already on ARVs is diagnosed with active TB, then treatment should not be discontinued. It may however need to be reviewed and changed so its effectiveness is not reduced by rifampicin. This applies most strongly if the treatment is based on protease inhibitors such as nelfinavir or indinavir.

According to World Health Organisation guidelines (Scaling up antiretroviral therapy in resource-limited settings guidelines for a public health approach), there are four options for antiretroviral regimens compatible with rifampicin, as follows:

Two nucleoside reverse transcriptase inhibitors (NRTIs) such as zidovudine (AZT) and didanosine (ddI) or lamivudine (3TC) plus

1. Efavirenz (EFV)
2. Nevirapine (NVP)
3. Saquinavir/Ritonavir
4. Abacavir

Efavirenz and rifampicin

In the case of efavirenz, rifampicin does slightly reduce the effective dose of EFV. Some authorities therefore advise increasing the dose of EFV from 600mg to 800mg a day. (There is detailed information on EFV and the other drugs mentioned here on aidsmap.com.) EFV is believed to be teratogenic and should not be given to pregnant women.

MARTIN: Our experience has been that increasing the dose of efavirenz to 800mg daily has been accompanied by a significant increase in CNS side effects. We have had satisfactory viral suppression using the 600mg dosage and PK studies are underway to provide an answer to the required dosing schedule.

Nevirapine and rifampicin

There is still some disagreement on the question of whether nevirapine-based ARV combinations, such as the fixed-dose combinations discussed in HATIP #2, can safely be combined with tuberculosis treatment. Rifampicin reduces drug exposure to nevirapine by 31%.

Considering the likely importance of nevirapine-based combinations as first-line ARV treatment in populations where TB is widespread, it is remarkable how little evidence there is, still, on the safety and efficacy of combining NVP with TB treatment and specifically with different dosing regimens of rifampicin. The results of such studies are keenly awaited.

REGENSBERG: We have had limited experience in using the two drugs together, but if the patient is already on a nevirapine-containing regimen and doing well, and is subsequently diagnosed with active tuberculosis, we recommend adding the standard rifampicin-containing regimen without any dose modification. We are concerned about shared hepatotoxicity however, so this should be carefully monitored. [Ideally, using liver enzyme blood tests.]

Saquinavir/ritonavir and rifampicin

WHO guidelines suggest that a combination of saquinavir with low-dose ritonavir can be used with rifampicin, but this is questionable. The Southern African HIV Clinicians Society recommends 400mg saquinavir/400mg ritonavir twice daily as the adult dosage. There is some evidence in support of this, according to Dr Anton Pozniak, although it is based on only two patients.

Saquinavir/ritonavir is preferred to ritonavir as a single agent as it reduces the dose of ritonavir to which patients are exposed, while making the saquinavir highly effective.

Ritonavir blocks the enzymes which are induced by rifampicin, but is an expensive drug and has to be stored in a refrigerator. It also is difficult for many people to tolerate, with gastro-intestinal and other side effects.

The low dose of ritonavir that is sometimes used to boost other protease inhibitors (e.g. indinavir, lopinavir) is definitely NOT sufficient to overcome the rifampicin effect, which makes it hard to understand why WHO recommends the use of such a combination with saquinavir.

Abacavir and rifampicin

Combinations of abacavir, an NRTI, with two other NRTIs (e.g. AZT, 3TC) are not ideal, despite the lack of interactions with rifampicin. The hypersensitivity reaction associated with abacavir is similar to the immune reconstitution syndrome seen with TB. As mentioned in HATIP #2, triple NRTI regimens are less effective than combinations based on efavirenz, at any level of viral load. They may be particularly weak when the viral load is high (above 100,000). People with HIV who have active TB are likely to have high viral load levels and if viral load tests are not available, this has to be assumed.

Working treatment out in practice

PRABHU: For patients who are suffering from TB in any form and diagnosed as HIV+ subsequently, we advocate ARV after the TB treatment is completed. If the CD4 counts and HIV viral load reports are available then a clinical decision is made based on the reports. The patients are counselled about the good effects of TB therapy, they are told they will gain in weight and improve appetite and their fevers will subside. Once the TB therapy takes hold and they symptomatically improve, they trust in the doctor and go along with the plan. They are periodically reviewed and after completion of TB regimen of 6 months, they are accessed a second time for the need to start ARV. In most instances they feel fine after TB treatment and ARV therapy is postponed till a subsequent date.

We try to avoid concurrent therapy with TB drugs during the entire phase of TB regimen. The uncertainty and possibility of drug failures and reduced levels of ARV drugs due to rifampicin levels and interaction with nevirapine, is a risk I definitely would not like to subject my patients to if I had a choice. Because the alternatives are not feasible. Ritonavir-based regimens are expensive, abacavir based triple NRTI's may not be potent and in an already febrile patient I would find it difficult to recognise abacavir toxicity, efavirenz regimens are supposed to be better than nevirapine but here again the effects are uncertain. If the patient can afford it, we may consider it worthwhile to put him on efavirenz during course of TB regimen. But as is often the case, it is not possible and so we prefer to wait and watch.

If a patient who is HIV positive on ARV develops TB, then we would question whether we are dealing with clinical virological failure of ARV. A thorough clinical history as regards duration and adherence to ARV medication is taken. History of contact with known TB patients or visits to TB hospices is made note of, in which case resistant TB is thought of. We normally do not expect HIV patients who are taking their ARV medication regularly to fall sick and are most worried when this happens! We try and get a CD4 and viral load test done, but if this is not possible, then TB regimen is started and we do not alter the existent ARV regimen in any way. Judging by the clinical response the next step is taken whether to alter the ARV regimen or continue with the present regimen. In most cases this decision has to be taken keeping in mind the financial resources and long term sustainability of the regimen. It is no point panicking and trying out all the available drugs in the market! Sometimes it is better to do nothing but to wait and watch and continue with nevirapine-based fixed dose combinations right through the TB regimen with no modifications.

Paediatric treatment

Diagnosis of TB in young children is more difficult than in adults, and treatment often relies for longer periods on rifampicin due to safety concerns about ethambutol. (The main concern with ethambutol is over its potential impact on eyesight, which is difficult to assess in very young children.) There is some disagreement between different guidelines, over the length of treatment advisable when children have HIV.

Henry Barigye observes that ritonavir boosted saquinavir is not likely to be used in children because of the size of the capsules. The liquid preparation of ritonavir is hardly available (and is very unpalatable).

Of the NNRTIs efavirenz (in tablet form) may also be difficult to take for small children.

His team's practice has therefore been to avoid giving ARVs during TB treatment. However, in a situation where the patient is very immunosuppressed the treatments will have to be combined.

"In the case of children we have relied on using nevirapine either as split tablets or as the suspension. In some cases (e.g. for re-treatment of TB) we have also had to use ethambutol in young children, in which case we use the lower end of the recommended dose range (15mg/kg)."

Dr Anton Pozniak observes that a presentation at last year's meeting of the International Union against TB and Lung Disease (IUTLD) reported positively on the safety of ethambutol in young children. Efavirenz is also increasingly being used in paediatric treatment.

The Canadian Paediatric Society's guidelines on TB treatment are a good model, available on the internet (see below) and easily adapted to limited-resource settings, which could usefully be compared with national guidelines.

Integrating TB and HIV treatment services

In North America and Western Europe, HIV treatment services generally developed quite independently of TB services. In countries where both diseases are widespread, there is an argument that large-scale HIV treatment services should ideally be established as an extension of TB treatment services.

As Professor Norman Nyazema observes: "We in Zimbabwe and I am sure the SADC region realized some time ago that HIV and TB control, prevention and care could no longer be separated given the

the epidemiology the two infections. We now have an HIV/TB unit serviced by an HIV/TB expert committee. The committee has representatives from the all disciplines including health education."

One concern about an integrated approach at a lower level is that social stigma may transfer from HIV to TB, threatening the effectiveness of TB services if people avoid TB treatment for fear of being seen as "having AIDS". The inclusion of VCT and HIV treatment in TB programmes, if done badly, can risk compromising both the voluntariness of VCT and quality in HIV treatment.

Dr Prabhu is surely right to point out that great care must be taken to separate patients who are coughing from patients (and healthcare workers) who are immunosuppressed. However, the risk of transmitting HIV in a clinical setting extends beyond those diagnosed with TB. A London outbreak of MDR TB occurred some years ago after sputum induction was carried out on an AIDS ward, on a patient who was not suspected at the time of having TB. So ALL investigations of lung disease must be carried out with precautions against cross-infection.

Also, in the setting of a large-scale combined epidemic where 70% or 80% of patients with TB may be HIV positive, can it be acceptable to ignore the possibility that TB patients need additional treatment, such as co-trimoxazole prophylaxis, as well as assessment for early access to ARVs?

PRABHU: I strongly feel that TB and HIV services need to be separated. Integrating both services is asking for disaster. Cross infection, outbreaks of TB, spread of resistant TB are just some of the nightmares any public health physician worth his salt would wish to avoid. To keep an immunocompromised individual, especially a healthy asymptomatic HIV patient, in a room of TB patients by integrating services is a great injustice and something which future generations will I am sure, judge us and hold us accountable. To compromise on this issue is not acceptable.

To send an HIV positive individual to a TB clinic is asking for trouble. The solution should be to bring DOTS to the HIV patient. To ensure access to TB drugs at the HIV clinic, private-public partnership has to be encouraged. HIV patients with symptoms need to be worked up and categorised as per WHO guidelines. The primary HIV physician should take responsibility and ensure that his patients have access to TB drugs through DOTS free of cost by collaborating with public sector officials, but that is more easily said than done.

HAUSLER: The South African Department of Health has developed a strategy for TB/HIV collaboration. The strategy recommends that TB and HIV/AIDS & Sexually Transmitted Infection programmes collaborate in the following areas: policy formulation, advocacy, health education, training, community mobilisation, surveillance and operational research. At district level this means establishing District TB/HIV Committees with TB/HIV and public/private partners, offering HIV counselling and testing to all TB patients, screening all HIV-positive clients for TB, providing co-trimoxazole prophylaxis to all HIV-positive TB patients, providing good management of opportunistic infections in TB facilities, ensuring that TB DOTS supporters provide HIV education, VCT

promotion and condom distribution, ensuring that home based carers provide DOTS. South Africa has just secured donor funding from the Belgian government and the Global Fund Against AIDS, TB and Malaria for phased implementation of these activities in all health districts in the country over the next 5 years.

Further information on aidsmap

Tuberculosis

[Rifampicin \(rifampin\)](#)

[Efavirenz - overview](#)

[Ritonavir - overview](#)

[Saquinavir/ritonavir - key research](#)

Other Internet resources

Dr Anton Pozniak's presentation on ARV treatment combined with TB treatment, [Pharmacology Resources / Antiretroviral Therapy / OIs: Co-managing HIV Infection and TB] on:

<http://www.hiv-druginteractions.org/>

Canadian Paediatric Society's 1994 guidelines (reaffirmed in 2000, updated in April 2002) on treatment of TB in children:

<http://www.cps.ca/english/statements/ID/id94-11.htm>

Factsheet on TB and HIV in South Africa, by Dr Harry Hausler

<http://www.journ-aids.org/TB%20and%20HIV-AIDS.htm>

Dr Richard Chaisson's webcast presentation at the Boston Retrovirus conference, Beyond DOTS: Approaches to Tuberculosis Control in Areas Where HIV Prevalence is High, is part of the Tuesday afternoon session on International Models and Perspectives in Addressing the Pandemic. To view this webcast, you need to have RealPlayer software installed on the computer - which is available as a free download but is a large program. The URL is:

<http://www.retroconference.org/2003/webcast.htm>

WHO Guidelines: Scaling up antiretroviral therapy in resource-limited settings

http://www.who.int/hiv/pub/prev_care/pub18/en/

WHO Treatment of Tuberculosis: Guidelines for National Programmes: <http://www.who.int/gtb/publications/ttgnp/>