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An integrated approach to HIV and TB care in adults in resource-limited settings, part 1

The immunological interaction

Tuberculosis has a significant effect upon the immune system, which is quite independent of and distinct from the effect of HIV. Initial MTB infection triggers the release of inflammatory blood chemicals such as TNF- α , IL-1 and IL-6, and the activation of macrophage and CD4 cells. This immune response cannot eradicate all TB bacilli from the body but in most cases, it does force the infection to retreat into latency inside scar nodules within the lungs. Clinical disease only occurs if the immune response cannot suppress the initial infection or upon reactivation. Roughly 5% of HIV-negative patients develop clinical disease within two years of MTB infection, and 5% more will go on to develop active disease sometime later in their life. Active TB has an overall dampening effect on the immune system, reducing CD4 cell counts and compromising responses to the extent that concurrent "opportunistic infections" are not uncommon, even without HIV.

TB accelerates HIV disease

Any opportunistic infection may accelerate HIV disease but in vitro studies have shown that the inflammatory immune response to MTB may greatly fuel HIV replication. What limited data are available in patients suggest that virus load is elevated in HIV-infected patients who are diagnosed with active TB and that viral load increases despite TB treatment. Active TB could also speed the decline in CD4 cell counts, increasing the likelihood of other concurrent opportunistic infections.

HIV's impact on TB

HIV infects CD4 cells (especially activated ones), leading to their depletion, which in turn limits the body's ability to control MTB. The immune response to MTB is so suppressed in some patients that their bodies lose the ability to detect a challenge from the infection. This is also known as anergy. When an individual becomes anergic, he or she can no longer mount a delayed hypersensitivity reaction (DTH) to tuberculin, the physiologic response that forms the basis of TB skin tests (see below in "HIV Coinfection confounds TB diagnostics").

The loss of an effective response to MTB in HIV positive patients dramatically increases their risk for active TB disease. While 10% of HIV-negative patients who are infected with MTB develop TB during their lifetime, more than 10% of coinfecting patients develop active disease each year. Active TB is also more likely to occur during or shortly after primary MTB infection. More than a third of the HIV-positive people who become newly infected with M. tuberculosis develop primary TB within six months of infection. Case fatality rates and TB recurrence are also more common among people with HIV. Reinfection is more likely as well.

HIV can change the clinical presentation of TB

TB can occur at any point during HIV disease. If TB occurs while CD4 cell counts are still relatively high, TB is usually the classic pulmonary infection with typical chest X-rays (CXR - see Diagnosis of Active TB below).

Patients with pulmonary TB commonly present with the following symptoms:

- Chronic (more than 2 weeks) cough that produces sputum (a "productive" cough)
- Breathlessness
- Fever and night sweats
- Appetite and weight loss
- Weakness and fatigue
- Chest pain or coughing up blood

Coinfected patients are much more likely to develop atypical pulmonary TB in which the almost any pattern of lung involvement can occur. Patients with this condition may not have a productive cough.

There is also a much greater risk of extrapulmonary TB that can involve any organ or tissue especially as CD4 cell counts fall.

Constitutional symptoms such as fever, fatigue and weight loss are fairly constant, but other symptoms are related to the site of the infection. Extrapulmonary conditions include:

- Tuberculous lymph node disease
- Bone and joint TB (osteitis). Spine involvement (myelopathy) is particularly dangerous.
- Pericardial TB: inflammation of soft tissue surrounding the heart. The condition puts great stress on the heart.
- Pleural TB: involving the membrane surrounding the lungs
- TB peritonitis: TB in the abdomen/gut, with swollen intra-abdominal lymph nodes and liver. Lymph nodes sometime adhere to the bowel causing obstructions and/or fistulae (fissures) between bowel, bladder and abdominal walls.
- Genitourinary TB involving the kidneys and urinary tract.
- TB meningitis: inflammation of the spinal cord or brain that can begin with irritability, sleeplessness, a stiff neck with headache that grows more severe, with increasing drowsiness, confusion/delirium, possible convulsions, decreased consciousness leading to coma or death.
- Disseminated TB (also miliary): a generalised systemic disease often with small nodules in affected organs and tissue.

These conditions may overlap or be concurrent. Effusions occur when affected tissues rupture and leak their contents (pus, lymphatic fluid, serous fluids) into surrounding areas.

Except when it is localised in the larynx, extrapulmonary TB is not thought to be highly infectious (since TB bacilli are spread through coughing). However, there may be a transient flare-up of TB in the lungs - some studies suggest that approximately twenty percent of patients with extrapulmonary TB are infectious at some point of their illness. But whether infectious or not, extrapulmonary TB should be treated because it can be life threatening.

HIV confounds TB diagnostic tests

Another result of the defective immune response to TB in coinfecting patients is that standard diagnostic tests for TB become unreliable.

This includes the test for diagnosing latent TB and conventional methods for diagnosing active TB.

Tuberculin or purified protein derivative (PPD) skin test

After the immune system forces primary MTB infection into latency, the body preserves some TB-specific CD4 cells to keep a memory of the infection in order to mount an effective response should MTB ever challenge the body again. This memory makes the standard test for exposure to TB possible.

The tuberculin or purified protein derivative (PPD) skin test detects whether the patient's immune system remembers MTB by injecting a small amount of a MTB protein into the skin. The immune system should recognise this as a challenge by a known foe and mount a response. A delayed hypersensitivity reaction (DHR) should be evident within a few days by the formation of a reddish or dark bump at the site of the injection. In adults, a bump of 5 mm or larger is considered to be positive.

However, some HIV-infected individuals cannot mount this response, either because their TB-memory CD4 cells have been eliminated by HIV or because HIV has somehow scrambled the signals that immune cells send each other. This lack of DHR is called "anergy." Anergy is more common in patients with advanced HIV disease and low CD4 cell counts. Antiretroviral therapy can sometimes restore the DHR in a patient, however.

Diagnosis of active pulmonary TB

HIV coinfection does not alter the gold standard for diagnosis: culturing. Growing TB mycobacteria from sputum in a culture can confirm diagnosis, but this takes weeks or months and requires specialised facilities that are not available in every setting. If possible, at least one good specimen should be sent to the regional reference laboratory for culturing and drug susceptibility testing. But treatment of active TB should not wait for culturing results.

Diagnosis and treatment is normally based upon a combination of other factors, including symptoms, CXRs and sputum AFB microscopy, all of which can be influenced by HIV infection.

Chest X-Rays (CXRs) in a patient with classic pulmonary TB usually show cavities in the upper lobes of the lung, but in patients with HIV, the CXR might appear normal, there may be cavitation in the lower lobes or the CXR may look similar to the effects of other lung infections. Importantly, there is no CXR pattern that firmly differentiates active TB from treated TB.

Sputum AFB microscopy

When a patient has classic pulmonary TB, coughed up sputum often contain MTB bacilli (which makes pulmonary TB infectious). If samples of sputum (called smears) are treated with a Ziehl-Neelsen or fluorochrome stain (medical dyes), acid-fast bacilli (AFBs) in the smear can be observed under a microscope. Usually, a diagnosis for pulmonary TB can be made on the basis of at least one or two positive results out of two or three smears. This test can be performed in most clinics' laboratories and plays a pivotal role in most TB control programmes.

But AFB microscopy is far less reliable in patients who are coinfecting. In some locations, over half the cases of active TB may be smear negative. Firstly, it can be very difficult to obtain sputum in a patient with HIV. One inexpensive way to increase the odds of getting a better specimen is to induce sputum or other bronchial fluids with hypertonic saline, using an ultrasonic nebuliser -

although not every care provider has access to a nebuliser. This must be done in well ventilated area or outside with the person doing the procedure wearing a protective mask because there is a risk of airborne transmission or spread to healthcare workers when inducing sputum.

But even induced sputum may be smear-negative in patients with HIV. In such cases, needle aspiration of neck lymph nodes or biopsied tissue from the lung may yield better specimens for microscopy. If AFB microscopy is still negative, the case should be referred to an experienced clinician who may make a presumptive diagnosis of TB and decide to offer empiric TB treatment if:

- There has been no response to a course of broad-spectrum antibiotics
- At least three sputum specimens are negative for AFB
- There are CXR abnormalities suggestive of TB

There should be a response to empiric anti-TB treatment (see below) usually within two months.

Diagnosis of extrapulmonary TB in people with HIV

Extrapulmonary TB is even more difficult to diagnose. It often requires invasive procedures to obtain diagnostic specimens from all clinically relevant tissues or fluids (including aspirated effusions, blood and urine) for AFBs, microscopy/histology, culture, and drug susceptibility testing (if possible). AFBs are easier to isolate from aspirated purulent or pleural effusions than from serous effusions. However, a high protein-content in serous effusions is suggestive of TB in a patient with HIV.

Diagnosis is usually presumptive, after excluding other possible conditions. Other clues to diagnosis follow by condition.

Tuberculous lymph node disease (TLD)

TLD must be distinguished from persistent generalised lymphadenopathy (PGL). In contrast to PGL, tuberculous lymph nodes are asymmetric, painful, grow quickly and are associated with other constitutional symptoms. A TB diagnosis can be made from a needle aspiration if the aspirated material is smear positive or caseated (cheesy). If inconclusive, a lymph node biopsy should be performed.

Bone and joint TB in the spine (TB Myelopathy)

CXRs of the spine will show disc space narrowing and erosion of the adjacent vertebrae.

Pericardial TB

Clues to TB diagnosis include rapid heart beat, low blood pressure, and distant heart sounds. There may be signs of right-sided heart failure eg: leg swelling, liver/spleen/abdominal swelling. CXRs may show an enlarged and spherical heart as well as serous and pleural effusions.

Pleural TB

Exclude for possible malignancies, post-pneumonic effusions and pulmonary embolisms. In patients with pleural TB, CXRs show a uniform white opacity, often with a concave upper border. Aspirated effusions produce a straw coloured exudate (secretion thick with solid material) with a high white blood cell count (1000 - 2500 per ml). If available, histological analysis of biopsied tissue greatly aids diagnosis.

TB peritonitis

The most likely differential diagnosis is spontaneous bacterial peritonitis (a common complication of cirrhosis of the liver) that can be excluded by aspirating the accumulated fluid in the ascites (peritoneal cavity) and evaluating the white blood cell content in the exudate. If TB, the white blood cells should be predominantly lymphocytes.

TB meningitis

A stiff neck and poor knee reflexes suggest meningeal inflammation. Tuberculosis meningitis can develop while patients are already on treatment for TB. A lumbar puncture should be performed to drain cerebrospinal fluid (CSF) for examination. The most likely differential diagnosis is cryptococcal meningitis, which should be excluded by conducting a cryptococcal antigen test, fungal culture or CSF microscopy, if possible.

Disseminated/miliary TB

Strongly associated with wasting. CXR may show scattered small nodules. Patients may have pancytopenia. Microscopy of CSF or bone marrow samples may also aid diagnosis. A urine sample taken early in the morning is often culture positive.

Empiric treatment of extrapulmonary TB should be followed closely, and the patient re-evaluated and monitored for signs of improvement every one to two weeks. Weight gain is a particularly important measurement of response.

Coinfection complicates medical management for both diseases

Prevention of active TB

Given the dramatically increased risk of active TB in patients with HIV, and the danger that active disease represents to them, it is important to try to prevent latent TB from reactivating.

A course of preventative TB therapy should be considered for patients with a positive PPD skin test. Prophylaxis (preventive treatment) should also be considered for some people with HIV who have negative PPD tests as some patients could be anergic or live or work in situations where exposure to TB is likely. Examples include anyone likely to come into contact with someone with pulmonary TB including healthcare workers and caregivers, household contacts (*especially children), miners and prisoners. TB prophylaxis should also be considered in patients with advanced disease who are about to begin antiretroviral treatment as they may harbour a subclinical and undetectable TB infection that can activate or trigger serious inflammation during initial immune reconstitution (see TB IRIS).

Before beginning TB prophylaxis, it is very important to exclude the possibility of active disease (Diagnosis of Active TB in People with HIV, by Syndrome below).

A number of regimens can reduce the risk of active TB in people with HIV, including:

- A six-month course of isoniazid (INH), a low-cost drug that can be taken at either 5 mg/kg daily to a maximum of 300 mg or 15 mg/kg twice weekly to a maximum of 900 mg twice a week. Pyridoxine (vitamin B6) is given along with isoniazid (25-50mg daily) to prevent liver toxicity and peripheral neuropathy. The duration of therapy is typically 6 months - even though studies have demonstrated that a 9-month course is superior to the

6-month course, there are concerns about decreased adherence with a longer duration of therapy.

- A three or four month rifampicin (RIF) with or without INH (sometimes as combination tablets).
- A two-month course of the combination of pyrazinamide (PZA) and RIF (usually as combination tablets) - recently, there have been reports of severe hepatic injury following this combination in HIV-negative patients.

INH regimens are by far the most common and widely used, particularly in patients on ART, as there are drug-drug interactions between rifampicin and certain antiretrovirals (see Drug Interactions below). RIF is the most potent sterilising anti-TB medication available so most programmes choose to reserve RIF for treatment of active disease (and thus reduce the likelihood of resistance). Although prophylaxis can eliminate latent TB infection, it does not prevent reinfection. Those in frequent contact with people with TB may need to repeat prophylaxis every couple of years.

Careful adherence to the treatment schedule is necessary to prevent the development of resistance. Prophylaxis should therefore only be given to patients who can be relied upon to take their medication correctly. However, TB prophylaxis should not be administered at TB clinics, lest patients with HIV be exposed to multi-drug-resistant tuberculosis (MDR-TB).

Treatment of active pulmonary TB

Generally, the standard TB regimen is the same for HIV-infected patients, with the exception that one of the lesser-used essential TB drugs, thioacetazone, is contraindicated as it can cause severe life-threatening skin-reactions in people with HIV.

In most settings, the treatment regimen for all adults with previously untreated tuberculosis consists of a 2-month initial phase (induction regimen) of daily (or five days weekly in some countries) INH 4-6 mg/kg, RIF 8-12 mg/kg, PZA 20-30 mg/kg and ethambutol (EMB) 15-20 mg/kg. These drugs are usually available in a fixed-dose combination tablet. Another essential TB drug, streptomycin, dosed at 15-20 mg/kg, is not so widely used due to toxicity, drug-resistance in some settings and because it must be administered as an injection.

A recent study has found that the daily induction regimen is superior to a three day a week regimen (<http://www.aidsmap.com/en/news/4346AD91-01A8-4760-AA4C-9D9B6C3BAC21.asp>).

Most clinicians start patients on vitamin B6 25-50 mg daily (to reduce INH side effects) and co-trimoxazole prophylaxis (which has been shown to decrease morbidity and mortality in HIV-infected tuberculosis patients).

After two months, if new smear results are negative, patients can be switched to a less intensive continuation phase. Different NTPs recommend different continuation phases based upon local (or individual) drug susceptibility patterns, drug availability and how closely patients can be monitored to ensure adherence.

There are two leading continuation phase regimens

- Four months of INH/RIF - this regimen has been shown to be superior (<http://www.aidsmap.com/en/news/4346AD91-01A8-4760-AA4C-9D9B6C3BAC21.asp>) but should only be given with support for adherence, such directly observed therapy (DOT) or equivalent intervention to prevent the development of resistance to rifampicin.

- Six months of INH/EMB, which can be given to patients with monthly follow-up

Some national guidelines recommend a five month continuation phase with three drugs (usually adding EMB) for some patients. Also NTPs differ on whether the drugs should be given daily, five or three days a week.

These drugs should also be given as a combination tablet wherever possible.

Treatment of extrapulmonary TB

Most experts now agree that virtually all forms of extrapulmonary TB can be treated with the regimens used for pulmonary disease, although in some cases a slightly longer duration treatment (9 months) may be advisable.

Corticosteroids have been shown to benefit patients some patients with extrapulmonary TB, in particular pericarditis and meningitis. They may also be of use in patients wasting and for airway obstruction due to lymph node compression/endobronchial disease.

Treatment of MDR TB

Some strains of TB have become resistant to one or more of the standard drugs. Multidrug-resistant (MDR-TB) strains exist in most parts of the world, and they are significantly more difficult to treat. MDR-TB treatment requires extra drugs: streptomycin, kanamycin, clarithromycin, amikacin, capreomycin, or a fluoroquinolone. These are more expensive, more toxic, less effective against TB and so a longer course of treatment is required. Drug selection in patients suspected to have MDR TB should be guided by history and local drug susceptibility patterns whenever possible. Usually, initial treatment is with the four-drug regimen plus at least additional 2 drugs to which the patient's MTB is thought to be susceptible. In patients with culture-confirmed MDR TB, at least 3 drugs the organism is susceptible to should be used for at least 12 months after the sputum conversion. Most experts recommend that treatment last 18 to 24 months.

TB Treatment, oral contraception and pregnancy

In pregnant women, HIV coinfection has also been associated with increased vertical transmission of HIV (and conversely, more frequent transmission of congenital TB). Treatment of latent and active disease is therefore important both for the health of the mother and her infant.

Oral contraception

RIF interacts with oral contraceptive medications and may reduce their efficacy. WHO recommends that women taking oral contraceptives and needing TB treatment should, after consultation with her clinician, either take a contraceptive pill with higher dose of estrogen (50 µg), or use another form of contraception.

Pregnancy

Pregnant women with active TB need to be treated with INH and RIF, which are safe during pregnancy. PZA, although recommended by many authorities, has not been thoroughly studied in pregnancy, and should be used at the discretion of the treating physician; EMB also has not been recommended. Streptomycin should not be used during pregnancy as it might damage the baby's hearing.

TB treatment and antiretroviral therapy

Coadministration of TB therapy and ART is complicated by drug interactions and the potential for additive toxicity. Furthermore, malabsorption of TB drugs occurs relatively frequently in AIDS patients and should be considered if there is little or no response.

RIF is a potent inducer of liver metabolism and reduces plasma levels of many drugs metabolised by the liver including non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors. Coadministration reduces the area under the curve (AUC) plasma levels of efavirenz by 22% and nevirapine by 37-58%. Trough levels of both NNRTIs remain therapeutic but are reduced.

However, there can be substantial variations in metabolism from one patient to another. Some of these variations are due to inherited differences in metabolism. For example, in one study metabolism of efavirenz was shown to be 28% higher in white non-Hispanics than in African-Americans and Hispanics. While some patients reductions in antiretroviral plasma levels could result in treatment failure.

A related drug rifabutin has much less of an effect on ART metabolism. It could also be substituted for rifampicin but it is either unavailable or too expensive for most NTPs to purchase. Streptomycin could also be substituted for rifampicin in anti-TB regimens but treatment would have to last at least 9-12 months to prevent relapse. Furthermore, globally many patients are resistant to streptomycin and the drug is inconvenient to administer.

Antiretroviral regimens may therefore need to be modified to be compatible with RIF-based tuberculosis treatment.

NNRTIs

While the CDC recommends increasing the efavirenz dose to 800mg daily, there are little or no published data on efavirenz metabolism in non-Western populations, but there is evidence of reduced efavirenz metabolism in non-white Americans. Thus some NTPs do not recommend increasing efavirenz dose when co-administered with rifampicin for fear of increased toxicity.

Nevirapine clearance also varies between ethnic groups but no dose adjustments are considered necessary.

Protease Inhibitors

Most protease inhibitor levels are significantly reduced when co-administered with RIF and should not be used, unless boosted by ritonavir in order to overcome liver enzyme induction of metabolism. However ritonavir is not heat-stable making it impractical in some settings. It also causes gastrointestinal intolerance. Side-effects may be eased by improved by gradual dose escalation over one week.

Nucleoside analogues

Nucs have no significant interactions with rifampicin. Formerly, abacavir-based triple nucleoside analog regimens were recommended. However, recent studies show that these regimens are inferior to conventional NNRTI/PI regimens.

Side-effects

There is also a risk of additive side-effects and drug toxicity when antiretrovirals are combined with TB treatment.

For example, hepatitis is a common side-effect of antiretroviral drugs (especially nevirapine) and INH, RIF, and PZA (especially INH).

In all patients with pre-existing liver disease, frequent clinical and laboratory monitoring should be performed to detect drug-induced hepatic injury. Drinking alcohol increases the risk of liver toxicity.

It may be advisable to switch patients who develop active TB while taking nevirapine-based ART to efavirenz. However, if the patient has been stable for more than two months, nevirapine can be continued while monitoring transaminase levels regularly.

Patients not yet taking ART who develop active TB

Patients with active TB not yet qualifying for ART should first be treated for TB. Their need for ART can be reassessed on completion of tuberculosis treatment - or sooner if there are signs of rapid clinical HIV/AIDS progression.

All HIV-infected patients with multi-drug resistant tuberculosis should be considered for antiretroviral therapy, even if CD4 >200 since prognosis is poor.

Recommendations vary for patients who do qualify for treatment (with less than 200 CD4 cells and/or AIDS-defining events). Some experts suggest that patients complete 2 months of anti-tuberculosis therapy before starting ART, due to the risks of additive side effects and drug toxicity.

However, a recent retrospective study suggests that the risk of death may be too great to postpone treatment for two months (see <http://www.aidsmap.com/en/news/6F731C18-27FF-45A5-9F5E-0DA7CDFB8322.asp>). Patients who present with advanced AIDS (for example CD4 < 50 cells or other serious opportunistic infections), ART may need to begin sooner - possibly as soon as their readiness for ART can be assessed.

Nevertheless, TB treatment should begin immediately.

TB immune reconstitution inflammatory syndrome

Some patients receiving antiretroviral therapy develop a syndrome known as TB Immune Reconstitution Inflammatory Syndrome or TB IRIS with apparent activation of TB or paradoxical worsening of TB symptoms. ART should be continued in these patients and most experts believe that patients should receive TB treatment even though patients with this syndrome are sometimes culture negative for TB.

The optimal treatment for TB IRIS needs to be evaluated in clinical trials, however, anecdotal data suggest a possible role for corticosteroid therapy.

These emerging issues thus call for more coordinated and collaborative approach of addressing the TB/HIV epidemic.

HIV's impact on TB control

Unfortunately, the growth of these two important epidemics of TB and HIV is happening together in many communities and countries. Although HIV may not make person with TB more infectious, a large increase in TB cases among HIV-positive people can increase the spread of TB overall. These emerging issues call for more coordinated and collaborative approach of addressing the TB/HIV epidemic that we intend to cover in more depth in the next issue of HATIP.

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