**HIV/TUBERCULOSIS CO-INFECTION**

**INTRODUCTION**

One third of the world's population are infected with tuberculosis (TB). More than half of the global TB burden is in the WHO South-East Asia and Western Pacific Regions, where, in 2003, there were 9.7 million prevalent cases of TB (291 per 100 000 populations) of which approximately five million were new cases.

**FIGURE 1:**

GLOBAL TB EPIDEMIOLOGY: TWENTY TWO COUNTRIES WITH A HIGH BURDEN OF TB (SHaded) SHARE 80% OF THE GLOBAL TB BURDEN

Of the estimated 44 million people living with HIV/AIDS, 12 million are co-infected with TB. The prevalence of HIV in patients with TB is 12% in Thailand and Cambodia, 6.8% in Myanmar and 4% in Viet Nam. Public health implications are profound. TB kills about 350 000 HIV patients every year, more than any other opportunistic infection (OI). The HIV epidemic fuels the TB epidemic by increasing the risk of reactivation of latent TB infection and by facilitating more rapid progression of TB disease. Unlike other OIs, TB can be readily transmitted to HIV negative household and other close contacts.

**TWO DISEASES, TWO TREATMENTS, ONE PATIENT**

Effective cooperation between TB and HIV programmes is essential for the management of HIV/TB co-infected patients. All patients diagnosed with TB should be encouraged to undergo counselling and testing for HIV. The challenges of treating HIV/TB co-infected patients include drug interactions and toxicities, immune reconstitution syndrome, high pill burden, adherence, stigma and discrimination related to HIV status.

**IMPACT OF HIV ON TB**

HIV is one of the strongest risk factors for developing active TB. While TB incidence is declining in the Western Pacific Region, rates of HIV/TB co-infection are increasing in sub-saharan Africa.

Patients with HIV infection are more susceptible to TB because immunodeficiency increases the risk of reactivation of latent TB infection and the risk of rapid progression of a recent TB infection. The risk of reactivating TB infection is 7-10% per annum in HIV infected persons compared to a less than 10% lifetime risk in those without HIV infection. Concurrent HIV infection is estimated to confer more than a 100 fold increased risk for development of active TB compared to HIV negative persons. Those with advanced HIV infection (WHO clinical stage 3 or 4) are at most risk of developing active TB infection.

**CLINICAL PRESENTATION**

Even in HIV-infected patients, pulmonary TB is the most common form of TB. In more advanced HIV infection, the typical TB chest X-ray findings of upper lobe infiltrates with cavitation are replaced by atypical findings of bilateral infiltrates (especially lower zones) with no cavitation. HIV-infected patients are more likely to present with a miliary pattern on chest X-ray and with hilar/mediastinal lymph node enlargement.
Diagnosis of TB in the presence of HIV infection is complicated by increased numbers of patients with pulmonary TB who are acid fast bacillus (AFB) smear negative.

Extrapulmonary TB is more common in HIV co-infection. Presentations include lymphadenopathy (usually cervical), pleural effusion, pericarditis, pericardial effusion, empyema and infections of the central nervous system (meningitis, tuberculoma), gastrointestinal tract, liver, kidney, adrenal glands, genital tract (orchitis, epididymitis, tubo-ovarian and endometrial infection), skin, bone and joint. TB recurrence rates among HIV positive patients are higher compared to those without HIV.

**IMPACT OF TB ON HIV**

TB is the most common OI and the most common cause of death among people living with HIV/AIDS. Unlike most other OIs, TB can occur at any point in the course of HIV infection and is not dependant on the CD4 lymphocyte count. However, the risk of developing active TB rises sharply with worsening immune status.\(^1\)

There is evidence that the host’s immune response to TB infection enhances HIV replication and accelerates the natural progression of HIV infection. The risk of death in HIV-infected patients with TB has been reported to be twice that in HIV infected patients without TB, independently of CD4 count.\(^8\) The high mortality rate among patients with TB appears to be due to progressive HIV infection rather than TB itself.\(^9,10\)

**MANAGEMENT OF TB DISEASE IN THE PRESENCE OF HIV INFECTION**

Current WHO guidelines recommend the same TB regimen for HIV/TB co-infected patients as is used in HIV negative TB infected patients.\(^11,12\).

Thioacetazone should not be administered to patients with HIV/TB co-infection due to increased risk of severe and potentially fatal skin reactions.\(^13,14\)

Fixed dose combinations of TB medications are preferred as they lower the pill burden and improve adherence.

**TABLE 1: TB DIAGNOSTIC CATEGORIES**

<table>
<thead>
<tr>
<th>TB diagnostic category</th>
<th>Patients</th>
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</table>
| **Category I**         | - New smear-positive pulmonary TB  
                          - New smear-negative pulmonary TB with extensive parenchymal involvement, concomitant HIV disease or severe forms of extrapulmonary TB |
| **Category II**        | Previously treated sputum smear-positive pulmonary TB:  
                          - relapse  
                          - treatment after default  
                          - treatment failure |
| **Category III**       | - New smear-negative pulmonary TB (other than Category I)  
                          - Less severe forms of extrapulmonary TB |
| **Category IV**        | Chronic and multi-drug resistance-TB (still sputum-positive after supervised re-treatment) |

A treatment regimen consists of two phases. The number before a phase is the duration of that phase in months.

b. This regimen may be associated with a higher rate of treatment failure and relapse compared to the 6-month regimen with rifampicin in the continuation phase.

Note: Direct observation of drug intake is required during their initial phase of treatment in smear-positive cases, and always in treatment including rifampicin.

**TREATMENT OF LATENT TB**

Isoniazid 300mg/day for six months is recommended by WHO for patients with latent TB infection following the exclusion of active TB disease by careful history taking, physical examination and chest X-ray. Other investigations (sputum culture) may be required to exclude active TB disease in symptomatic patients.

**MANAGEMENT OF TB IN HIV-INFECTED CHILDREN**

Regimens and drug dosages (mg/kg) are the same for children as for adults. As with adults, thioacetazone should not be administered to HIV-infected children.

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**TABLE 2: RECOMMENDED TREATMENT REGIMENS FOR EACH DIAGNOSTIC CATEGORY**

<table>
<thead>
<tr>
<th>TB Diagnostic Category</th>
<th>Initial phase</th>
<th>Continuation phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>2 HRZ&lt;sup&gt;c&lt;/sup&gt;</td>
<td>4HR or 6HE daily&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>II</td>
<td>2HRZES and 1HRZE</td>
<td>5HRE</td>
</tr>
<tr>
<td>III</td>
<td>2HRZE</td>
<td>4HR or 6HE daily&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>IV</td>
<td>Specially designed individualized cases (are suggested for this category)</td>
<td></td>
</tr>
</tbody>
</table>

H=Isoniazid, R=rifampicin, Z=Pyrazinamide, E=Ethambutol, S=streptomycin


**DRUG INTERACTIONS**

Rifampicin induces the cytochrome P450 liver enzyme system, which metabolizes protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs). This can lead to decreased blood levels of these antiretrovirals and failure of HIV treatment. This interaction is clinically most relevant in developing countries where rifampicin is widely available (rifabutin is not) and first-line antiretroviral usually includes efavirenz or nevirapine. Nevirapine levels are reduced by 37% and efavirenz levels by 25%-33% in the presence of rifampicin.

Four abstracts at the 6th International Workshop on Clinical Pharmacology of HIV Therapy (28-30 April 2005, Quebec, Canada) presented more on rifampicin NNRTI interactions but still did not resolve the issues. While some data (mostly in patients with body weights close to 50 kg) supports standard efavirenz dosing (600mg/day), the dose of EFZ may need to be increased to 800 mg/day. Data on the use of NVP and rifampicin are similarly limited and conflicting. This regimen should only be used when no other options are available.

**MANAGEMENT OF HIV IN THE PRESENCE OF TB**

The recommended first-line ARV regimen is

**Stavudine or Zidovudine**

+ **Lamivudine**

+ **Efavirenz**

If available, tenofovir or abacavir may be substituted for stavudine and zidovudine. Standard doses of stavudine and lamivudine are given with TB drugs, but in the absence of definitive recommendations, efavirenz may need to be increased to 800 mg per day.
The patient may be switched from EFV to NVP once rifampicin is ceased. If patients are switched from EFV to NVP, no lead-in dosing of NVP is necessary. Start with NVP 200 mg BID. If a rifampicin containing regimen is used for six months (initial and continuation phases) EFV-based ARV should be used for the whole time the patient is taking rifampicin.

EFV is contraindicated in pregnant women or women of childbearing potential without effective contraception. Alternatives are saquinavir/r or abacavir containing regimens. Patients with HIV/TB co-infection require clinical monitoring by physicians experienced in the management of both diseases. The optimum time at which to commence ARV in a patient with HIV/TB co-infection is unknown and studies are ongoing. Persons infected with HIV who begin taking antiretroviral agents early in the course of their anti-TB therapy are more likely to experience the immune reconstitution syndrome, which is characterized by exacerbation of symptoms and signs or by radiographic manifestations of TB.18

**TABLE 3:**
**CURRENT WHO RECOMMENDATIONS ON WHEN TO INITIATE ARV IN PATIENTS WITH HIV/TB CO-INFECTION**

<table>
<thead>
<tr>
<th>Patient clinical status</th>
<th>No CD4 available</th>
<th>CD4 available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary TB only (no other signs of WHO Clinical Stage III or IV)</td>
<td>Start and complete TB treatment, then start antiretroviral treatment</td>
<td><strong>If CD4 &gt; 350</strong>&lt;br&gt;Start and complete TB treatment, then start ART unless non-TB Stage IV conditions are present (start earlier if present, based on clinical judgement)</td>
</tr>
<tr>
<td>Pulmonary TB and patient has or develops other signs of Stage III or IV</td>
<td>Start TB treatment. Timing of ART initiation should be based on clinical judgement in relation to other signs of immunodeficiency</td>
<td><strong>If CD4 between 200-350</strong>&lt;br&gt;Start TB treatment. Start ART after initiation phase of TB treatment (start earlier if severely compromised).</td>
</tr>
<tr>
<td>Extrapulmonary TB</td>
<td>Start TB treatment. Start ART as soon as TB treatment is tolerated (between 2 weeks and 2 months), irrespective of CD4</td>
<td><strong>If CD4 &lt; 200</strong>&lt;br&gt;Start TB treatment. Start ART as soon as TB treatment is tolerated (between 2 weeks and 2 months).</td>
</tr>
</tbody>
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**IMMUNE RECONSTITUTION SYNDROME (DISEASE)**

Immune reconstitution syndrome (IRS) is characterized by the appearance of signs and symptoms of an opportunistic disease following commencement of potent antiretroviral therapy (ART) in the setting of advanced immunodeficiency. The syndrome typical occurs within 6-12 weeks on ART in patients with low CD4 counts (50-100 cells/mm³). It may present as mycobacterium avium complex (MAC), lymphadenitis or bacteraemia, TB paradoxical reactions, cryptococcal meningitis, CMV retinitis, herpes zoster or herpes simplex disease or HCV/HBV hepatotoxicity.

Patients with HIV-related TB may experience a temporary exacerbation of symptoms, signs or radiographic manifestations of TB after beginning TB treatment. Such paradoxical reactions were noted in the pre-HIV era. In the era of effective ARV therapy, these reactions have been reported to occur at a rate of between 5% and 36%.19,20

The syndrome is characterized by fever, lymphadenopathy, worsening of pulmonary lesions on CXR examination and expanding CNS lesions. These reactions are typically self-limiting and TB and ARV therapy should be continued. A brief course of corticosteroids may be required to reduce inflammation for severe respiratory or CNS symptoms.

The risk of immune reconstitution syndrome may be reduced by delaying the introduction of ARV until the completion of the initial two-month phase of TB therapy in patients who have initial CD4 count > 200 cells/mm³.

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HOW TO STRENGTHEN THE COLLABORATION BETWEEN TB AND HIV PROGRAMMES: THE WHO INTERIM POLICY ON COLLABORATIVE TB/HIV ACTIVITIES

BACKGROUND
The Interim Policy responds to a demand from countries for immediate guidance on which collaborative HIV/TB activities to implement and under what circumstances. It is complementary to and in synergy with the established core activities of tuberculosis and HIV/AIDS prevention and control programmes. Implementing the directly-observed treatment, short course (DOTS) strategy is the core activity for tuberculosis control. Similarly, infection and disease prevention, health promotion activities, and the provision of treatment and care form the basis for HIV/AIDS control.

PURPOSE
The Interim Policy is designed to help decision-makers in the field of health, tuberculosis and HIV/AIDS programme managers working at all levels in the health sector, as well as donors, development agencies and nongovernmental organizations supporting tuberculosis and HIV/AIDS programmes. The recommendations made in this document also have important implications for the strategic directions and activities of other ministries.

RATIONALE
The HIV pandemic presents a massive challenge to the control of TB at all levels. Tuberculosis is also one of the most common causes of morbidity and one of the leading causes of mortality in people living with HIV/AIDS. This document will assist policy-makers to understand what should be done to decrease the joint burden of tuberculosis and HIV. This policy does not call for the institution of a new specialist or independent disease control programme. Rather, it promotes enhanced collaboration between tuberculosis and HIV/AIDS programmes in the provision of a continuum of quality care at service-delivery level for people with, or at risk of, tuberculosis and people living with HIV/AIDS.

While there is good evidence for the cost-effectiveness of the DOTS strategy and several HIV prevention measures, the evidence for collaborative HIV/TB activities is limited and is still being generated in different settings. Existing evidence from randomized controlled trials, non-randomized trials and other analytical and descriptive observational studies, operational research and expert opinion based on sound clinical and field experience was used for this interim policy document. It is a rolling policy, which will be continuously updated to reflect new evidence and best practices.

POLICY FORMULATION PROCESS
The Global TB/HIV Working Group contributed to the formulation of this policy, with a writing committee preparing its initial and subsequent versions. The Working Group coordinates the global response to the intersecting tuberculosis and HIV epidemics, forging collaboration between the HIV/AIDS and tuberculosis communities. Its membership includes programme managers, development agencies, nongovernmental organizations, academic institutions, activists and patient-support groups working with WHO and the Joint United Nations Programme on HIV/AIDS (UNAIDS) on both tuberculosis and HIV programmes. The writing committee included technical experts from tuberculosis and HIV, policy-makers involved in health management, persons living with HIV and their advocates; international and national tuberculosis and HIV programme managers, and donor agencies.

The draft policy has been discussed at international conferences by international and national stakeholders in HIV and TB programmes and it has been endorsed by the Global TB/HIV Working Group and the Strategic and Technical Advisory Group for tuberculosis (STAG), which provides WHO with external strategic and technical advice on tuberculosis control. The policy goal is to decrease the burden of HIV and TB in populations affected by both diseases. The objectives of collaborative HIV/TB activities are: (1) to establish the mechanisms for collaboration between TB and HIV/AIDS programmes; (2) to decrease the burden of tuberculosis in people living with HIV/AIDS; and (3) to decrease the burden of HIV in tuberculosis patients.

This Interim Policy focuses on collaborative activities that address the interface of TB and the HIV/AIDS epidemics and that should be carried out as part of the health sector response to the intersecting TB and HIV epidemics (Table 1).
TARGETS FOR COLLABORATIVE HIV/TB ACTIVITIES

The WHO global tuberculosis target is to cure 85% of sputum-smear positive patients under treatment and to detect 70% of cases by 2005.

The United Nations General Assembly Special Session on AIDS (UNGASS) has set the following targets:

- By 2005, reduce HIV prevalence among young men and women (15-24 years) in most affected countries by 25% and reduce HIV prevalence by 25% globally by the year 2010.
- By 2005, ensure that at least 90% of young men and women (15-24 years old) have access to youth-specific information, education and communication materials on HIV/AIDS and that by 2010 this proportion has raised to at least 95%.
- By 2005, reduce the proportion of infants infected with HIV by 20% and by 50% in 2010.

By developing effective collaboration and implementing joint activities, HIV/TB will contribute to achieving these targets. Nevertheless, there is limited evidence to show the exact magnitude and the mechanism by which these collaborative activities will contribute to achieve these targets. As a consequence a high level of caution should be exercised in setting quantified targets for collaborative HIV/TB activities.

WHO’S FRAMEWORK TO ADDRESS TB-HIV CO–INFECTION IN THE WESTERN PACIFIC REGION

HIV is having a dramatic impact on TB control in countries with a high burden of TB/HIV. At the same time, tuberculosis is not only the leading cause of death among people with AIDS, but is also the most common curable infectious disease among people with HIV/AIDS.

While in sub-Saharan Africa the HIV epidemic is having a devastating impact on the TB epidemic, the proportion of new TB cases infected with HIV among all TB cases in most countries in the Western Pacific Region is still relatively low. Although the HIV/TB problem has not yet reached epidemic proportions in the Region, there is clear evidence that the rising number of HIV infections increasingly affects the TB prevalence in the Western Pacific Region.

In response to the threat of TB-HIV, the Stop TB and HIV/AIDS units in the WHO's Western Pacific Regional Office developed the Regional framework to address TB-HIV, fitting with the Region's epidemiological situation and health care setting. The rationale of the Regional framework is that tackling tuberculosis should include tackling HIV as the most potent force driving the tuberculosis epidemic; and tackling HIV should include tackling tuberculosis as a leading killer of people with HIV/AIDS.

The Regional framework, which draws on the Global strategic framework to reduce the burden of HIV/TB21 and on the Interim policy on collaborative HIV/TB activities22 is built on the strengths of the individual national TB and AIDS programmes, and identifies areas in which both programmes complement each other in addressing HIV/TB. Key components of the Regional framework are: surveillance; intensified case finding (diagnosis and referral, including voluntary counseling and testing (VCT) for HIV); prevention, treatment and care; and, areas of collaboration.

The framework outlines the roles of the individual TB and HIV/AIDS programmes ("who does what") and provides examples of how to operationalize the different components.

### TABLE 4:
RECOMMENDED COLLABORATIVE HIV/TB ACTIVITIES

<table>
<thead>
<tr>
<th>(1) Establish the mechanisms for collaboration.</th>
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<tbody>
<tr>
<td>(a) Set up a coordinating body for HIV/TB activities effective at all levels.</td>
</tr>
<tr>
<td>(b) Conduct surveillance of HIV prevalence among tuberculosis patients.</td>
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<tr>
<td>(c) Carry out joint HIV/TB planning.</td>
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<tr>
<td>(d) Conduct monitoring and evaluation.</td>
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<table>
<thead>
<tr>
<th>(2) Decrease the burden of tuberculosis in people living with HIV/AIDS.</th>
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</thead>
<tbody>
<tr>
<td>(a) Establish intensified tuberculosis case-finding.</td>
</tr>
<tr>
<td>(b) Introduce isoniazid (IPT) preventive therapy.</td>
</tr>
<tr>
<td>(c) Ensure tuberculosis infection control in health care and congregate settings.</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>(3) Decrease the burden of HIV in tuberculosis patients.</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) Provide HIV testing and counseling.</td>
</tr>
<tr>
<td>(b) Introduce HIV prevention methods.</td>
</tr>
<tr>
<td>(c) Introduce co-trimoxazole preventive therapy.</td>
</tr>
<tr>
<td>(d) Ensure HIV/AIDS care and support.</td>
</tr>
<tr>
<td>(e) Introduce antiretroviral therapy.</td>
</tr>
</tbody>
</table>

REFERENCES


HIV/AIDS
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