Providing HIV care for co-infected tuberculosis patients: a perspective from sub-Saharan Africa

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SUMMARY

Human immunodeficiency virus/acquired immunedeficiency syndrome (HIV/AIDS) and tuberculosis (TB) are overlapping epidemics that cause an immense burden of disease in sub-Saharan Africa. This region is home to the majority of the world’s co-infected patients, who have higher TB case fatality and recurrence rates than patients with TB alone. A World Health Organization interim policy has been developed to reduce the joint burden of TB-HIV disease, an important component of which is provision of HIV care to co-infected patients. This review focuses on HIV testing of TB patients and, for those who are HIV-positive, the administration of adjunctive cotrimoxazole preventive treatment (CPT) and antiretroviral treatment (ART). HIV testing has moved from a voluntary, client-initiated intervention to one that is provider-initiated and a routine part of the diagnostic work-up. The efficacy and safety of CPT in HIV-infected patients is now well established, and this is an essential part of the package of HIV care. ART scale-up in Africa can substantially improve outcomes in co-infected patients. However, the clinical and programmatic challenges of combining ART with anti-tuberculosis treatment need to be resolved to realise the full potential of this benefit. These include the optimal time to start ART, how best to combine rifampicin-containing regimens with first-line and second-line ART regimens, management of immune reconstitution disease, the role of isoniazid preventive treatment with ART after TB treatment completion, and where and how to provide combined treatment to best suit the patient. Clinical and operational studies in the next few years should help to resolve some of these issues.

KEY WORDS: HIV; TB; Africa; ART; cotrimoxazole
unless additional strategies and interventions are put in place. Under the leadership of the World Health Organization (WHO) and the Stop TB Partnership, TB-HIV guidelines, a TB-HIV strategic framework and an interim TB-HIV policy have all been developed to reduce the burden of TB-HIV disease in severely affected countries. One of the main prongs of the TB-HIV interim policy is to reduce the impact of HIV in co-infected patients. This review will focus on three important interventions: provider-initiated HIV testing and counselling, cotrimoxazole preventive treatment (CPT) and antiretroviral treatment (ART).

### THE IDEAL PACKAGE OF CARE FOR THE CO-INFECTED PATIENT

Once a patient is diagnosed with TB, HIV testing and counselling should be offered if the HIV status is unknown or was previously reported as negative. If a patient previously tested HIV-positive, but there is no documented evidence, the test should be repeated, as in most African countries a patient can only access CPT and ART if there is proof of a positive HIV test result. Ideally, HIV testing is performed soon after the diagnosis of TB, before, during or just after the process of registration and start of anti-tuberculosis treatment. If the patient is HIV-positive, he/she should be screened and treated for active opportunistic infections and offered CPT as soon as possible, provided there are no contraindications. The patient can then be considered for ART. The Figure highlights the main steps in providing HIV care to the co-infected patient.

### HIV TESTING AND COUNSELLING OF TB PATIENTS

**Voluntary counselling and HIV testing**

The traditional approach to HIV testing, the only approach in vogue for many years, is voluntary counselling and testing (VCT). The decision is left entirely with the client or patient about whether to have the test, and the emphasis is on extensive pre-test counselling and the social and preventive implications of being HIV-infected or knowing one’s serostatus. This type of intervention has been shown in East Africa to promote behaviour change and reduce sexual transmission of HIV.

**Provider-initiated HIV testing**

In 2002, De Cock and colleagues argued that HIV/AIDS in Africa should be redefined as a public health and infectious disease emergency and that there should be an increased focus on treatment, advocating for routine and diagnostic HIV testing within health care settings. This approach differs from VCT in that HIV testing is requested by the health care worker and is an integral part of the clinical interaction. There is greater emphasis on ‘opting out’ (patients undergo an HIV test as part of the diagnostic work-up unless they specifically decline), and there is a higher priority on post-test rather than pre-test counselling, particularly if the patient is HIV-positive. Routine and diagnostic HIV testing is now usually promoted as ‘provider-initiated’ (opt-out) testing.

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**Table 1** The WHO Interim Policy of reducing the joint burden of HIV and TB

<table>
<thead>
<tr>
<th>Prevent TB in people living with HIV</th>
</tr>
</thead>
<tbody>
<tr>
<td>• TB infection control in health care and congregate settings</td>
</tr>
<tr>
<td>• Intensified TB case finding</td>
</tr>
<tr>
<td>• Isoniazid preventive treatment</td>
</tr>
<tr>
<td>• Scale-up of antiretroviral treatment</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treat HIV in patients with TB</th>
</tr>
</thead>
<tbody>
<tr>
<td>• HIV testing and counselling</td>
</tr>
<tr>
<td>• Cotrimoxazole preventive treatment</td>
</tr>
<tr>
<td>• Antiretroviral treatment</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Establish collaboration between HIV and TB programmes</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Activities include setting up coordinating bodies at all levels, surveillance of HIV prevalence in TB patients, joint planning and resource mobilisation, training, supervision, monitoring and evaluation</td>
</tr>
</tbody>
</table>

* Adapted from reference 10. WHO = World Health Organization; HIV = human immunodeficiency virus; TB = tuberculosis.
treatment and care and 3) preventing onward transmission of HIV. The latter may be achieved through disclosure of HIV status, HIV testing of partners, reducing risky behaviours, making condoms readily available in TB services and clinics, screening and treating sexually transmitted infections and preventing unintended pregnancies and mother-to-child transmission. In various reports, provider-initiated HIV testing for TB patients appears feasible and acceptable and is associated with high rates of uptake. From 2001 onwards, rapid HIV test kits were introduced, replacing cumbersome HIV enzyme-linked immunosorbent assay (ELISA) tests, and these have facilitated the feasibility of and access to HIV testing for both provider and client.

Despite the obvious advantages of HIV testing, the routine uptake among TB patients has been slow. The Global Plan to Stop TB provides annual targets for TB-HIV control, with particular attention being given to HIV testing of TB patients and enrolling HIV-positive patients on ART. In sub-Saharan Africa, by the end of 2006, 737 000 TB patients should have been HIV tested. Data for 2006 are not yet available, but at the end of 2005 only 17% of these 737 000 TB patients had been tested, suggesting that the target for 2006 will not be met unless there is a significant improvement in field activity. This may now be happening, with Malawi and South Africa (personal observations), Kenya, Rwanda and Zambia reporting large increases in the uptake of HIV testing by TB patients in 2006 and 2007.

Provision of HIV testing for all TB patients will require much better functioning health systems than is currently the case to ensure uninterrupted supplies of HIV test kits, adequate numbers and commitment of counsellors and TB care providers, and reliable and regular monitoring systems. Easier ways of embedding HIV testing and counselling into the process of TB diagnosis or TB treatment registration should also be considered, with HIV testing performed before (for TB suspects) or at the point of TB diagnosis in wards or clinics or carried out as an essential and integral part of TB treatment registration. This approach, sensitively handled, might positively influence patient and provider perception of ‘two diseases, one patient’ and facilitate better access to TB-HIV interventions.

**COTRIMOXAZOLE PREVENTIVE TREATMENT FOR TB PATIENTS**

Although there are no annual targets for CPT in the Global Plan to Stop TB, CPT is an integral part of the WHO TB-HIV interim policy and an important intervention that, on its own, can save lives. Cotrimoxazole (trimethoprim-sulphamethoxazole) is a widely available, cheap and safe antibiotic, which has a broad spectrum of activity against several HIV-related and non-HIV-related pathogens. In industrialised countries, it is widely used for primary and secondary prophylaxis against *Pneumocystis jirovecii* pneumonia (PJP) and *Toxoplasma gondii* encephalitis.

In Africa, CPT was hardly considered until a randomised controlled study from Cote d’Ivoire in 1999 showed a 48% mortality reduction in HIV-positive TB patients given CPT compared with placebo. There were also significantly fewer hospital admissions due to septicaemia and enteritis. CPT was well tolerated, with only 1% of patients having skin reactions. A smaller study from South Africa, published shortly after the Cote d’Ivoire study, showed that CPT in HIV-positive TB patients was associated with an increase in survival of approximately 60%. The Cote d’Ivoire study persuaded the WHO and the Joint United Nations Programme for HIV/AIDS (UNAIDS) to issue provisional recommendations that CPT be given to all patients in Africa living with AIDS, including HIV-positive patients with TB.

Despite these recommendations, routine use of CPT in sub-Saharan Africa remained minimal due to: 1) concerns about lack of efficacy in countries with already high rates of bacterial resistance to cotrimoxazole (rates of resistance were low in Cote d’Ivoire at the time of the original study); 2) a possible upsurge in community rates of bacterial resistance to cotrimoxazole; and 3) a possible increase in the resistance of malaria parasites to sulphadoxine-pyrimethamine (SP), which is still used as first-line treatment for malaria in several endemic countries. However, in the last few years, these concerns have been largely answered by clinical studies and trials.

**Clinical studies and trials on CPT in Africa**

In two rural districts in Malawi, a package of HIV testing, counselling and CPT as an adjunct to antituberculosis treatment was associated with a 19% reduction in mortality compared with historical controls, the number needed to treat to prevent one death in both district-based studies being 12 patients. In South Africa, where rates of dual TB-HIV infection were nearly 80%, CPT given to all TB patients, irrespective of HIV status, showed an overall mortality reduction of 29% compared with historical controls, the number needed to treat to prevent one death being 24 patients. Although not conducted solely in TB patients, a before-and-after-study in Uganda of CPT in HIV-positive individuals showed a 46% reduction in mortality, the number needed to treat to prevent one death being eight patients. Major benefits of CPT in Uganda were observed, although over three-quarters of isolated pathogens causing diarrhoea were resistant to cotrimoxazole. Significant benefits from CPT were observed in patients whose CD4 cell counts were >500/mm³, leading to the conclusion that CPT is useful in all HIV-infected patients, irrespective of CD4 cell count. In Lusaka, Zambia, where resistance to cotrimoxazole is between 60%
above 200/mm³, at which levels PJP and be stopped once ART has brought CD4-cell counts to CPT? In industrialised countries, CPT would normally reduction in mortality, with the reduction in mortality occurred across all ages and CD4 cell counts.33 ART is given for life, but what about life expectancy, particularly if treatment was guided by bianing CPT with ART resulted in significant gains in redared in early 6-month mortality compared with using ART alone.32 In Cote d’Ivoire, a strategy of combining CPT with ART together resulted in fewer malaria episodes compared with using CPT alone.31 In Malawi, CPT started living in settings that have yet to access ART or whose children aged 5–15 years was associated with excellent protective efficacy against malaria and did not select for SP-resistant parasites.29

Guidelines for use of CPT in HIV-infected patients, including those with TB

CPT therefore works even in areas with high rates of bacterial resistance. WHO guidelines endorse the use of CPT in HIV-infected adults and children in resource-limited settings, and provide advice about dosages, contraindications, management of side effects and when to discontinue medication (Table 2).30 In addition to reducing morbidity and mortality, CPT is a useful intervention for HIV-infected TB patients living in settings that have yet to access ART or whose CD4 cell counts are considered too high for initiation of ART. Furthermore, CPT could lay the foundation for medication adherence prior to ART.31 The future operational challenges are how to ensure uninterrupted provision of CPT to all co-infected patients and how to monitor usage and benefit.

Combining CPT with ART

There appears to be added benefit in combining CPT and ART. In HIV-infected adults in Uganda, CPT and ART together resulted in fewer malaria episodes compared with using CPT alone.32 In Malawi, CPT started simultaneously with ART was associated with a 40% reduction in early 6-month mortality compared with using ART alone.33 In Cote d’Ivoire, a strategy of combining CPT with ART resulted in significant gains in life expectancy, particularly if treatment was guided by CD4 cell counts.33 ART is given for life, but what about CPT? In industrialised countries, CPT would normally be stopped once ART has brought CD4-cell counts to above 200/mm³, at which levels PJP and T. gondii encephalitis are rare. However, the same reasoning may not apply in Africa where rates of malaria, bacterial infections and diarrhoea are high and CPT provides a protective effect. Current WHO advice is that CPT, once started, should be given indefinitely if CD4 counts are not available for patient monitoring, but consideration can be given to discontinuing CPT if follow-up CD4 counts rise above the threshold for starting CPT and provided adherence to ART has been good.30

Table 2 Guidelines on use of cotrimoxazole preventive treatment

<table>
<thead>
<tr>
<th>Policy recommendations</th>
<th>Adults</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td>CPT for all symptomatic HIV-positive adults (WHO Stages 2, 3 and 4)</td>
<td>CPT for all children born to HIV-positive mothers</td>
</tr>
<tr>
<td>Children</td>
<td>CPT for HIV-positive adults with CD4 count of &lt;500 cells/mm³</td>
<td>CPT for all HIV-positive children aged &lt;5 years, regardless of symptoms</td>
</tr>
<tr>
<td>Adults</td>
<td>CPT for all symptomatic HIV-positive children aged &gt;5 years</td>
<td>CPT for all symptomatic HIV-positive children aged &gt;5 years</td>
</tr>
</tbody>
</table>

Dosages of cotrimoxazole

<table>
<thead>
<tr>
<th>Dosages of cotrimoxazole</th>
<th>Adults</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td>480 mg twice a day (1 tablet twice daily) or 960 mg once daily (1 double-strength tablet once daily)</td>
<td>Children aged 6–14 years: 480 mg once a day (1 tablet once daily) Children aged 6 months—5 years: 240 mg once a day (1/2 tablet once daily) Children aged 6 weeks—6 months: 125 mg once a day (1/4 tablet once daily)</td>
</tr>
</tbody>
</table>

Contraindications for CPT

<table>
<thead>
<tr>
<th>Contraindications for CPT</th>
<th>Adults and children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td>Known allergy to cotrimoxazole or sulpha drugs</td>
</tr>
<tr>
<td>Children</td>
<td>First trimester of pregnancy for pregnant women</td>
</tr>
</tbody>
</table>

Discontinuation of CPT

<table>
<thead>
<tr>
<th>Discontinuation of CPT</th>
<th>Adults</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td>Discontinue CPT in the event of severe cutaneous reactions, renal or hepatic disease or severe haematological toxicity</td>
<td></td>
</tr>
<tr>
<td>Children</td>
<td>Discontinue CPT in the event of severe cutaneous reactions, renal or hepatic disease or severe haematological toxicity</td>
<td></td>
</tr>
</tbody>
</table>

One of the most commonly used first-line ART regimens currently used in sub-Saharan Africa is a fixed-dose combination of stavudine (d4T) + lamivudine (3TC) + nevirapine (NVP), with which CPT has no significant additive adverse reactions. However, due to d4T toxicity, the WHO is promoting more use of zidovudine (AZT), which is potentially haematotoxic, as is cotrimoxazole. Additive toxicity may therefore become an issue in the future.

ANTIRETROVIRAL TREATMENT FOR HIV-INFECTED TB PATIENTS

In 1995, ART transformed AIDS in the industrialised world from a fatal infectious disease into one that is potentially chronic and manageable.34 Despite additive adverse effects and paradoxical reactions, HIV-infected TB patients in industrialised countries have greatly improved survival outcomes and excellent
virological responses to ART. In the last few years, African countries have been scaling up ART: by December 2006, an estimated 1.340,000 patients had been placed on ART in sub-Saharan Africa. HIV-positive patients with TB are all potentially eligible for ART, because patients with pulmonary TB (and children with TB lymphadenitis) are classified in WHO Clinical Stage 3 and patients with extra-pulmonary TB in WHO Clinical Stage 4. There is thus every reason to expect that ART will reduce TB case fatality and recurrent TB in co-infected patients.

The recommended anti-tuberculosis treatment regimens for new patients with TB are shown in Table 3. In HIV-positive TB patients, the key tenets of anti-tuberculosis treatment are: 1) the need for daily rifampicin (RMP) during the initial phase; 2) the use of RMP, where possible, in the continuation phase (this leads to lower failure and relapse rates compared with isoniazid [INH] and ethambutol); and 3) a RMP-containing continuation phase that is given at least three times weekly (to prevent relapse and development of RMP resistance). The development of multidrug-resistant TB (MDR-TB) requires the use of a combination of a minimum of four effective drugs (Table 4). Combining anti-tuberculosis drugs with antiretroviral (ARV) drugs, both first- and second-line (Table 5), is not easy, and the difficulties encountered in the field have resulted in fewer patients than expected accessing ART. By the end of 2005, an estimated 25,000 HIV-infected TB patients had been placed on ART against a 2006 target of 220,000. These difficulties have to be overcome, as the benefits of combined treatment are substantial. In a comparatively well-resourced urban cohort in South Africa, with good adherence support, excellent immunological and virological outcomes are achievable under programme conditions. The issues around combined treatment are discussed below.

**Timing of ART in co-infected patients who have started anti-tuberculosis treatment**

The optimal time to start ART in HIV-positive TB patients is an important but complicated issue, and there are arguments for early as well as delayed treatment.

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### Table 3 First-line anti-tuberculosis drugs and regimens for new patients

<table>
<thead>
<tr>
<th>Initial phase of treatment (daily or 3 times a week)</th>
<th>Continuation phase of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>New patients</td>
<td></td>
</tr>
<tr>
<td>2EHRZ (SHRZ)</td>
<td>6HE</td>
</tr>
<tr>
<td>2EHRZ (SHRZ)</td>
<td>4HR</td>
</tr>
<tr>
<td>2EHRZ (SHRZ)</td>
<td>4H3R1†</td>
</tr>
<tr>
<td>Previously treated patients (relapse, treatment after interruption, treatment failure)</td>
<td>2SEHRZ/5SHR2E3†</td>
</tr>
</tbody>
</table>

* The number before a phase is the duration of that phase in months. An alternative drug (or drugs) appears as a letter (or letters) in brackets.
† A number in subscript after a letter is the number of doses of that drug per day.
E = ethambutol; H = isoniazid; R = rifampicin; Z = pyrazinamide; S = streptomycin.

### Table 4 Second-line anti-tuberculosis drug regimens

A combination of:
- Any first-line drugs to which drug susceptibility is retained
- A fluoroquinolone (ofloxacin or moxifloxacin)
- An injectable agent (capreomycin, kanamycin or amikacin)
- Other second-line drugs, such as cycloserine, ethionamide or para-aminosalicylic acid

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### Table 5 Antiretroviral agents/regimens in common use in sub-Saharan Africa

<table>
<thead>
<tr>
<th>Nucleoside reverse transcriptase inhibitors</th>
<th>Nucleotide reverse transcriptase inhibitors</th>
<th>Non-nucleoside reverse transcriptase inhibitors</th>
<th>Protease inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zidovudine (AZT)</td>
<td>Tenofovir (TDF)</td>
<td>Nevirapine (NVP)</td>
<td>Nelfinavir (NFV)</td>
</tr>
<tr>
<td>Lamivudine (3TC)</td>
<td></td>
<td>Efavirenz (EFV)</td>
<td>Saquinavir (SQV)</td>
</tr>
<tr>
<td>Stavudine (d4T)</td>
<td></td>
<td></td>
<td>Ritonavir (RTV)</td>
</tr>
<tr>
<td>Abacavir (ABC)</td>
<td></td>
<td></td>
<td>Lopinavir (LPV)</td>
</tr>
<tr>
<td>Emtricitabine (FTC)</td>
<td></td>
<td></td>
<td>Indinavir (IDV)</td>
</tr>
</tbody>
</table>

A combination of:
- Stavudine + lamivudine + nevirapine
- Stavudine + lamivudine + efavirenz
- AZT 300 mg + 3TC 150 mg + NVP 200 mg (all twice a day)
- AZT 300 mg + 3TC 150 mg (twice a day) + EFV 600 mg (once a day)
- AZT 300 mg + 3TC 150 mg (twice a day) + EFV 600 mg (once a day)
- Tenofovir + lamivudine + lopinavir/ritonavir
- TDF (once a day) + 3TC (AZT) (twice a day) + LPV/RTV (twice a day)
- Didanosine + abacavir + lopinavir/ritonavir
- ddl (once a day) + ABC (once or twice a day) + LPV/RTV (twice a day)
**Table 6** Early vs. late ART for co-infected patients

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Start ART early: 2–8 weeks after start of anti-tuberculosis treatment during the initial phase</td>
<td>• High pill burden and poor drug adherence</td>
</tr>
<tr>
<td>• May reduce early TB-HIV morbidity and mortality, which is high in the first 2 months of anti-tuberculosis treatment</td>
<td></td>
</tr>
<tr>
<td>• May improve sputum smear conversion rates</td>
<td></td>
</tr>
<tr>
<td>• May be an advantage in drug-resistant TB</td>
<td></td>
</tr>
<tr>
<td>Start ART later: 8 weeks after start of anti-tuberculosis treatment during the continuation phase</td>
<td>• May have limited impact on TB case fatality because many HIV-infected TB patients who will die do so in the first 2 months of anti-tuberculosis treatment</td>
</tr>
<tr>
<td>• Patient more stable</td>
<td></td>
</tr>
<tr>
<td>• Pill burden less</td>
<td></td>
</tr>
<tr>
<td>• Continuation phase may not have rifampicin, using isoniazid and ethambutol instead</td>
<td></td>
</tr>
<tr>
<td>• Less risk of immune reconstitution disease</td>
<td></td>
</tr>
</tbody>
</table>

This presents clinical challenges, particularly in very under-resourced settings. In Malawi, for example, where ART was started in small numbers of co-infected patients in the second week of anti-tuberculosis treatment, clinical management was difficult and complicated by adverse effects, immune reconstitution disease (IRD) or new illnesses. In contrast, in better resourced settings such as South Africa, early start of ART has not been overly problematic. The issue of when to start ART still needs further evaluation, but it is likely that the survival benefit that might come with early initiation of ART would outweigh the poorer eventual outcomes associated with delays in initiating ART.

### Additive adverse effects

ARV drugs and anti-tuberculosis drugs may cause overlapping toxicity (Table 8). Additive drug toxicity compromises patient safety and is an important cause

**Table 7** World Health Organization recommendations about when to start ART in TB patients

<table>
<thead>
<tr>
<th>CD4 cell count/mm³</th>
<th>ART recommendations</th>
<th>Timing of ART in relation to start of TB treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;200</td>
<td>Recommend ART</td>
<td>Between 2 and 8 weeks (in initial phase of TB treatment)¹</td>
</tr>
<tr>
<td>200–350</td>
<td>Recommend ART</td>
<td>After 8 weeks (in continuation phase of TB treatment)</td>
</tr>
<tr>
<td>&gt;350</td>
<td>Defer ART</td>
<td>Re-evaluate the patient at 8 weeks and at the end of TB treatment</td>
</tr>
<tr>
<td>Not available</td>
<td>Recommend ART</td>
<td>Between 2 and 8 weeks</td>
</tr>
</tbody>
</table>

¹ As soon as possible within this time frame for those with the most advanced immune deficiency.

**Table 8** Additive adverse drug reactions between anti-tuberculosis drugs and ART drugs

<table>
<thead>
<tr>
<th>Adverse reaction</th>
<th>Main ARV drug involved</th>
<th>Main anti-tuberculosis drug involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral neuropathy (early or late side effect)</td>
<td>Stavudine</td>
<td>Isoniazid</td>
</tr>
<tr>
<td>Hepatitis (usually an early side effect. This is a major problem when combining rifampicin and second-line risonavir-boosted protease inhibitor regimens)</td>
<td>Nevirapine</td>
<td>Rifampicin</td>
</tr>
<tr>
<td>Gastrointestinal dysfunction, e.g., diarrhoea, abdominal pain (early or late side effect)</td>
<td>All</td>
<td>All</td>
</tr>
<tr>
<td>Skin rash (usually early side effect)</td>
<td>Nevirapine</td>
<td>Rifampicin</td>
</tr>
<tr>
<td>Central nervous system dysfunction (early or late side effect)</td>
<td>Efavirenz</td>
<td>Isoniazid</td>
</tr>
<tr>
<td>Anaemia (usually early side effect)</td>
<td>Zidovudine</td>
<td>Pyrazinamide</td>
</tr>
</tbody>
</table>

ART = antiretroviral treatment; TB = tuberculosis; HIV = human immunodeficiency virus.
of discontinuation of ART and interruptions of TB and/or HIV treatment.

d4T used in standard dosages is a well-recognised cause of peripheral neuropathy, the risk increasing with concurrent use of INH.46 This can be partly prevented or treated by ensuring that the patient also takes pyridoxine.

NVP is the non-nucleoside reverse transcriptase inhibitor (NNRTI) most likely to cause hepatotoxicity and skin reactions, with the risk being increased in women with CD4 counts >250 cells/mm³, men with CD4 counts >400 cells/mm³ and patients with a body mass index of <18.5.47,48 Up to 10% of co-infected patients may have CD4 cell counts >350 cells/mm³ at the time of starting treatment,49 and, with the lack of access to CD4 count testing in many African settings, one in ten patients may be at increased risk of NVP-induced toxicity. RMP, pyrazinamide and INH further increase this risk.48 Rates of treatment-limiting toxicity are greater when combining NVP with RMP compared with combining efavirenz (EFV) with RMP,50 and for this reason EFV is the preferred NNRTI in patients receiving anti-tuberculosis treatment.38

Pharmacokinetic interactions with first-line ART regimens

NNRTIs are metabolised mainly through cytochrome P450 (CYP450) enzymes. The rifamycins (RMP, rifapentine and rifabutin [RFB]) are potent inducers of this enzyme system, with RMP having the greatest effect and RFB the least, and they therefore cause reductions in plasma concentrations of NNRTIs. RMP reduces the plasma concentrations of NVP by 30–40% and EFV by 20–25%,51,52 and there is concern that if drug levels are sub-therapeutic, this will lead to drug resistance and treatment failure.

There are various ways of dealing with this problem. First, the dose of NVP could be increased from 200 mg to 300 mg twice daily:53 however, not only is this option difficult to implement when fixed-dose combination regimens are used, but the risk of drug-induced toxicity is also significantly increased. Second, EFV could be substituted for NVP. EFV is generally well tolerated, but the drug is potentially teratogenic (and at least half of treated patients are women), there is currently no fixed-dose generic combination with d4T and 3TC, and the drug is costly. There was debate about whether the dose of EFV should be 600 mg or 800 mg daily. However, excellent virological outcomes are achievable using the standard 600 mg dose of EFV,42,54 and this is what is now recommended in international guidelines.38,40 Third, RFB causes less reduction in levels of NNRTIs,55 and this could replace RMP. However, RFB is not available in fixed-dose combinations, it has haematological side effects and it is currently too expensive. Finally, abacavir (ABC) and tenofovir (TDF) are NRTIs that can both be given with AZT and 3TC as triple or quadruple nucleoside/nucleotide regimens that have no clinically significant pharmacokinetic interaction with RMP. Although these triple/quadruple NRTI regimens are effective, they are largely untried in co-infected TB patients, there are concerns about their potency, ABC can cause life-threatening hypersensitivity and they are expensive.52

Despite their shortcomings, both NVP and EFV appear to have a broad therapeutic index and evidence has shown that patients receiving standard dosages concurrently with RMP have good clinical, immunological and virological outcomes.42,51,52 A small, but important point is that the lead-in phase of NVP (200 mg daily for the first 2 weeks) in the presence of RMP results in nearly 60% of plasma NVP levels being sub-therapeutic,45 and this practice should be avoided when RMP-based treatment is used, as virological outcomes have also been shown to be undermined.50 At present, EFV is the recommended NNRTI of first choice,38,40 but due to expense and a lack of suitable fixed-dose combinations, NVP will still be used concurrently with anti-tuberculosis treatment regimens until further evidence becomes available to suggest otherwise.

Pharmacokinetic interactions with second-line ART regimens

In the same way as NNRTIs, protease inhibitors (which are the cornerstone of second-line ART, Table 5) are metabolised through CYP450 enzymes. In addition, RMP increases the activity of the efflux multidrug transporter P-glycoprotein (P-gp), which contributes to the elimination of protease inhibitors. RMP reduces levels of unboosted protease inhibitors such as nelfinavir, indinavir or atazanavir by more than 80%,40 and these therefore cannot be used together. The problem can be overcome to some extent by using ritonavir (RTV) boosted protease inhibitors, although the doses of RTV required to produce therapeutic levels of protease inhibitors are typically much higher than are usually used. Several studies have investigated the use of lopinavir and saquinavir with high-dose RTV, but there is substantial interpatient variability, with some patients experiencing inadequate blood levels and some experiencing severe drug toxicity.40,56

RFB is an alternative to RMP that can be used with most protease inhibitors (with or without RTV boosting), but, for the reasons discussed above, the use of RFB in Africa is at present almost non-existent. Until further data are available, if a first-line ART regimen has failed and the patient is on anti-tuberculosis treatment, clinicians may consider completing anti-tuberculosis treatment before switching to second-line ART.

Immune reconstitution disease

It has long been recognised that anti-tuberculosis treatment in HIV-negative patients can be associated with a transient worsening of clinical disease a few days or weeks after initiation of treatment.57 However, the frequency of these reactions is greatly increased by
 concurrent use of ART, and these demonstrate a strong temporal relationship with ART initiation. The pathogenesis of these IRD events is believed to be due to the restoration of cell-mediated immunity in response to mycobacterial antigens. This increasingly recognised phenomenon causes diagnostic and management challenges (Table 9). IRD has been reported to occur in up to one third of TB patients initiating ART in high-income settings, and most commonly presents with fever, worsening respiratory manifestations and lymphadenopathy. However, reports from resource-poor countries to date have found lower rates of around 10%. In the only published study from sub-Saharan Africa, the timing of ART initiation was the over-riding determinant of risk: patients starting in the first month of anti-tuberculosis treatment had a 70-fold greater adjusted risk of developing IRD compared with patients starting ART beyond 3 months of treatment. Although some patients with TB-IRD die, the background mortality risk of these patients is also high, as they typically have very advanced immunodeficiency. Thus, in the study from South Africa, the development of TB-IRD was not associated with an excess mortality risk. As yet, there is no real evidence base for the management of TB-IRD and outcomes from randomised controlled trials are eagerly awaited.

Adjunctive treatment with isoniazid after completion of anti-tuberculosis treatment
In HIV-positive patients who have successfully completed anti-tuberculosis treatment, INH preventive treatment (secondary IPT) for 6–12 months effectively reduces the risk of recurrent TB. ART reduces the risk of developing TB in HIV-positive patients, and the magnitude of this benefit may increase over the first few years of treatment. Recent data from Brazil in HIV-infected clients who have not developed TB confirm the benefit of ART and IPT on their own, but importantly show that ART and IPT together result in a highly significant 76% decline in risk of active TB. Whether IPT courses should be repeated (as protective efficacy wanes with time) and whether post-TB treatment IPT confers any added advantage to long-term ART are not known, and data are required from randomised controlled trials.

Where to provide anti-tuberculosis treatment and ART
In many African countries, ART is delivered in hospital clinics, while anti-tuberculosis treatment is delivered in the continuation phase from health centres as a result of decentralised management over the last 5–10 years. The logistic and financial difficulties that patients encounter in visiting health centres to collect anti-tuberculosis drugs and then hospitals to collect ART drugs are a major reason for the poor access of co-infected patients to ART. In countries with good TB-HIV programmes, fewer than a third of patients access ART. Solutions include better geographical access to ART through expansion of clinics to rural areas; consideration of ‘one-stop shops’, i.e., clinics where patients can receive both medications at the same time with either an ART clinic providing anti-tuberculosis treatment or a TB clinic providing ART, and more involvement of established community structures to deliver TB treatment and ART.

MDR-TB, XDR-TB and ART
MDR-TB (defined as resistance to at least INH and RMP) results from deficiencies in TB case management and programme control, and there is growing evidence of an overlap between this epidemic and HIV. This was dramatically illustrated by the report in 2006 of a nosocomial outbreak of extensively drug-resistant TB (XDR-TB, caused by MDR strains also resistant to quinolones plus one of the injectable second-line agents) in KwaZulu Natal, South Africa. Mortality rates in patients co-infected with HIV and MDR- or XDR-TB are very high, even in specialised management programmes. ART, perhaps given at an earlier stage in anti-tuberculosis treatment than is the case for drug-susceptible TB, should improve the prognosis of HIV-related drug-resistant TB, although there are no data to confirm this. Second-line anti-tuberculosis drugs are associated with considerable adverse effects that overlap with those of ART drugs (Table 8), although the absence of RMP from the regimens does simplify the issue to some extent. Access to diagnostics for the early diagnosis of drug-resistant TB and the prevention of nosocomial/community-based transmission of drug-resistant TB among HIV-infected persons remain major challenges: these are topics too extensive to be covered in this article.

CONCLUSION
TB-HIV co-infected patients have poor outcomes if just treated with DOTS regimens. The addition of provider-initiated HIV testing, CPT and ART should greatly improve prognosis. HIV testing and initiation
of CPT are straightforward, and what is now required of national programmes is the commitment and resources to overcome the logistic hurdles of offering this package to all co-infected patients. Although excellent outcomes are achievable, the administration of ART to patients on anti-tuberculosis treatment is still fraught with management challenges. These need to be resolved through clinical and operational research if optimal benefit of ART is to be obtained. Future treatment would be made considerably easier if there were wider availability of EFV in fixed-dose combinations, for example TDF, 3TC and EFV as a once daily fixed-dose combination; cheaper generic fixed-dose formulations of rifabutin for use with second-line protease inhibitor based regimens; replacement of d4T by TDF; and finally, new and effective anti-tuberculosis drugs that have fewer interactions with ART. The introduction and scale-up of ART in sub-Saharan Africa has changed the environment in which we operate, and we should now make the most of this opportunity to reduce the suffering and death that has hitherto been caused by the twin epidemic of HIV and TB.

References


La infección por el virus de la inmunodeficiencia humana y el síndrome de inmunodeficiencia adquirida (VIH/SIDA) y la tuberculosis (TB) provocan epidemias superpuestas que dan origen a una carga de morbili-
dad considerable en África subsahariana. En esta región ha-
bita la mayor cantidad de personas infectadas y presen-
tan una mortalidad por TB y tasas de recaídas más altas que los pacientes que padecen exclusivamente la TB. La Organización Mundial de la Salud elaboró una política interina con el propósito de reducir la carga de morbi-
dad conjunta de la infección por el VIH y la TB, uno de
los principales componentes es la provisión de cuida-
dos de la infección por el VIH a pacientes coinfectados.
El presente estudio analiza en primer lugar la realización
de la prueba diagnóstica de infección por el VIH en pa-
cientes tuberculosos y el suministro de tratamiento pre-
ventivo con cotrimoxazol (CPT) y de tratamiento anti-
retroviérico (ART). Se evolucionó de la política de prueba
serológica del VIH voluntaria por iniciativa del usuario,
a la prueba por iniciativa del proveedor de atención de
salud y a la prueba como parte del estudio sistemático.

Actualmente, se encuentran bien establecidas la efica-
cy la seguridad toxicológica del CPT en pacientes in-
fettados por el VIH, y este constituye una parte esencial
 del cuidado de la infección por el virus. La expansión del
ART en África puede mejorar en forma considerable el
desenlace clínico de los pacientes infectados. Sin em-
bargo, existen dificultades clínicas y programáticas en
la asociación del ART y el tratamiento antituberculoso,
que deben resolverse a fin de obtener todo el beneficio
posible de esta medida. Entre los problemas se encuen-
tran definir el momento óptimo para comenzar el ART,
la mejor manera de asociar las pautas con rifampicina
y los ART de primera y segunda línea, el tratamiento del
síndrome de reconstitución inmune, la utilidad de la pro-
filaxis con isoniazida con el ART tras la compleción del
tratamiento antituberculoso y dónde y cómo prover el
tratamiento combinado que se acomode mejor a las ne-
cesidades del paciente. La realización de estudios clínicos
y operativos en los próximos años debería ayudar a re-
solver algunas de estas dificultades.

**RESUMÉ**

Le virus de l’immunodéficience humaine/syndrome de
l’immunodéficience acquise (VIH/SIDA) et la tuber-
close (TB) sont des épidermes qui se superposent et qui
représentent un fardeau immense de maladie en Afrique
sub-saharienne. Cette région est le site de la majorité des
patients co-infectés au niveau mondial, chez lesquels la
létalité par TB et le taux de rechute sont plus élevés par
parallèle avec les patients atteints uniquement de
TB. Une politique intermédiaire de l’Organisation Mon-
diale de la Santé a été élaborée pour réduire le fardeau
conjoint de la maladie VIH-TB, avec comme compo-
sante importante la fourniture de soins VIH aux patients
co-infectés. Cette revue se concentre sur les tests VIH
chez les patients TB et chez ceux qui sont séropositifs
pour le VIH, sur l’administration conjointe d’un traite-
ment préventif au cotrimoxazole (CPT) et d’un traite-
ment antirétroviral (ART). Les tests VIH sont passés
de l’intervention volontaire initiée par les patients à
une intervention initiée par le pourvoyeur de soins
comme élément du travail de diagnostic de routine. Il est

Bien établi aujourd’hui que la CPT chez les patients in-
fettés par le VIH est efficace et sûre et qu’elle constitue
une part essentielle de l’ensemble des soins VIH. L’exten-
sion de l’ART en Afrique peut améliorer de manière
substantielle les résultats chez les patients co-infectés.
Toutefois, il faut résoudre les défis cliniques et program-
matiques de la combinaison de l’ART avec le traitement
antituberculeux pour atteindre le potentiel maximal de
ce traitement. Ces éléments comportent le moment
optimal du début de l’ART, la meilleure façon de combi-
nérer les régimes à base de rifampicine avec les régimes
de première et de deuxième ligne de l’ART, la prise en
charge de la maladie de reconstitution immunitaire, le
rôle de la chimioprévention à l’isoniazide en combinai-
son avec l’ART après l’achèvement du traitement de
la TB ainsi que le lieu et la façon de fournir un traitement
conjoint pour répondre au mieux aux convenances du
patient. Des études cliniques et opérationnelles à conduire
dans les quelques prochaines années devraient aider à
résoudre certains de ces problèmes.

**RESUMEN**

La infección por el virus de la inmunodeficiencia hu-
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