INT J TUBERC LUNG DIS 13(1):6–16

STATE OF THE ART SERIES
Tuberculosis
Edited by I. D. Rusen
NUMBER 3 IN THE SERIES

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

A. D. Harries,*† R. Zachariah,‡ S. D. Lawn†§

*** International Union Against Tuberculosis and Lung Disease, Paris, France; † Department of Infectious and Tropical Diseases, London School of Hygiene & Tropical Medicine, London, UK; ‡ Operational Research Unit, Medical Department, Brussels Operational Centre, Médecins sans Frontières, Brussels, Belgium; § Institute for Infectious Disease and Molecular Medicine, Desmond Tutu HIV Centre, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa**

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 patents, 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

SUB-SAHARAN AFRICA bears the brunt of the overlapping epidemics of the human immunodeficiency virus (HIV) and tuberculosis (TB). Countries in southern Africa are particularly affected, with over 50% of TB patients diagnosed each year being co-infected with HIV.[1,2]

HIV-TB co-infected patients treated only with standardised anti-tuberculosis chemotherapy have poor outcomes compared with patients who only have TB. Case fatality rates are higher,[3] and in patients who complete treatment there is a higher rate of recurrent TB.[4] Treatment outcomes are worse due to several factors: stigma leading to delays in seeking care and thus more advanced disease at the time of presentation to health services; difficulties in making an accurate diagnosis of smear-negative TB;[5] HIV-associated morbidity; drug-related side effects;[6] and higher rates of nosocomially acquired drug-resistant TB,[7] which in the routine setting takes too long to diagnose or may not be diagnosed at all.

The DOTS strategy on its own is inadequate for the optimal management of co-infected patients, and the TB-specific Millennium Development Goals of reducing the prevalence and death rates of TB by 50% by 2015 will not be achieved in high HIV-burden areas

Previous articles in this series **Editorial:** Rusen I D. Tuberculosis State of the Art series. Int J Tuberc Lung Dis 2008; 12(11): 1223. **No. 1:** Davies P D O, Pai M. The diagnosis and misdiagnosis of tuberculosis. Int J Tuberc Lung Dis 2008; 12(11): 1226–1234. **No. 2**: Landry J, Menzies D. Preventive chemotherapy. Where has it got us? Where to go next? Int J Tuberc Lung Dis 2008; 12(12): 1352–1364.

Correspondence to: A D Harries, International Union Against Tuberculosis and Lung Disease, 68 boulevard St Michel, Paris, France. Tel: (+33) 1 44 32 03 60. Fax: (+33) 1 43 29 90 87. e-mail: adharries@theunion.org

[A version in French of this article is available from the Editorial Office in Paris and from the Union website www.theunion.org]

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

Prevent TB in people living with HIV
• TB infection control in health care and congregate settings
• Intensified TB case finding
• Isoniazid preventive treatment
• Scale-up of antiretroviral treatment
Treat HIV in patients with TB
• HIV testing and counselling
• Cotrimoxazole preventive treatment
• Antiretroviral treatment
Establish collaboration between HIV and TB programmes
• 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

* Adapted from reference 10.
WHO = World Health Organization; HIV = human immunodeficiency virus; TB = tuberculosis.

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,[8] a TB-HIV strategic framework[9] and an interim TB-HIV policy (Table 1)[10] 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.[11] 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.[12] This type of intervention has been shown in East Africa to promote behaviour change and reduce sexual transmission of HIV.[13]

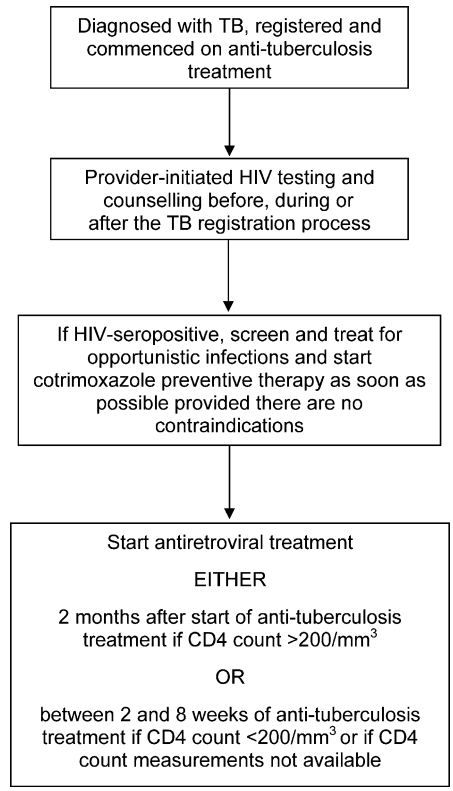

Figure HIV care for the co-infected patient with tuberculosis. TB = tuberculosis; HIV = human immunodeficiency virus.

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.[14] 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.[15]

HIV testing for TB patients

HIV testing for TB patients is indicated for several reasons: 1) establishment of the diagnosis of HIV, 2) a gateway to an adjunctive package of HIV clinical

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.[16] In various reports, provider-initiated HIV testing for TB patients appears feasible and acceptable and is associated with high rates of uptake.[2,12,17] 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.[18] 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.[2]

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.[11] 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.[19] 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.[20] 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%.[21] 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.[22]

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.[17,23] 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.[24] 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.[25] 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 $>500/mm^3$, 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%

and 80%, a randomised placebo-controlled trial in children showed that CPT was associated with a 43% reduction in mortality, with the reduction in mortality occurring across all ages and CD4 cell counts.[26]

There is an increase in bacterial resistance to cotrimoxazole among TB patients taking CPT.[27] However, a household study in Uganda provided reassuring evidence that use of CPT among HIV-infected individuals did not lead to an increase in bacterial resistance to cotrimoxazole amongst family members.[28] Although cotrimoxazole and SP have similar mechanisms of action and resistance patterns, a randomised controlled study in Mali showed that CPT in 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.[19] 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.[31] In Malawi, CPT started simultaneously with ART was associated with a 40% reduction in early 6-month mortality compared with using ART alone.[32] 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/mm^3, 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

Policy recommendations	
Adults	CPT for all symptomatic HIV-positive adults (WHO Stages 2, 3 and 4) CPT for HIV-positive adults with CD4 count of ⩽500 cells/mm^3
Children	CPT for all children born to HIV-positive mothers CPT for all HIV-positive children aged <5 years, regardless of symptoms CPT for all symptomatic HIV-positive children aged ⩾5 years
Dosages of cotrimoxazole	
Adults	480 mg twice a day (1 tablet twice daily) or 960 mg once daily (1 double-strength tablet once daily)
Children	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)
Contraindications for CPT	
Adults and children	Known allergy to cotrimoxazole or sulpha drugs First trimester of pregnancy for pregnant women
Discontinuation of CPT	
Adults	Discontinue CPT in the event of severe cutaneous reactions, renal or hepatic disease or severe haematological toxicity
Children	In HIV-exposed infants (i.e., children born to HIV-positive women), CPT should be taken until HIV infection can confidently be excluded. At 18 months of age, and provided the child has stopped breast-feeding, the child should have an HIV test. If the child continues to breast-feed after 18 months, CPT is continued until 3 months after breast-feeding has stopped and the child is then offered an HIV test. In both situations, if the HIV test is positive, then the child continues on CPT. If the HIV test is negative, then the child discontinues CPT Discontinue CPT in the event of severe cutaneous reactions, renal or hepatic disease or severe haematological toxicity

CPT = cotrimoxazole preventive treatment; HIV = human immunodeficiency virus; WHO = World Health Organization.

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

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

Initial phase of treatment (daily or 3 times a week)	Continuation phase of treatment
New patients	
2EHRZ (SHRZ)	6HE
2EHRZ (SHRZ)	4HR
2EHRZ (SHRZ)	$4H_3R_3$†
Previously treated patients (relapse, treatment after interruption, treatment failure)	
2SEHRZ/1EHRZ	5HRE/$5H_3R_3E_3$†

* 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 week. If there is no number in subscript after a letter, then treatment with that drug is daily.
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

virological responses to ART.[35,36] 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.[37] 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.[38,39] 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).[40] The development of multidrug-resistant TB (MDR-TB) requires the use of a combination of a minimum of four effective drugs (Table 4).[41] Combining anti-tuberculosis drugs with antiretroviral (ARV) drugs, both first- and second-line (Table 5),[38,40] 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.[2] 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.[42] 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

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

A Antiretroviral agents

Nucleoside reverse transcriptase inhibitors	Nucleotide reverse transcriptase inhibitors	Non-nucleoside reverse transcriptase inhibitors	Protease inhibitors
Zidovudine (AZT)	Tenofovir (TDF)	Nevirapine (NVP)	Nelfinavir (NFV)
Didanosine (ddI)		Efavirenz (EFV)	Saquinavir (SQV)
Lamivudine (3TC)			Ritonavir (RTV)
Stavudine (d4T)			Lopinavir (LPV)
Abacavir (ABC)			Indinavir (IDV)
Emtricitabine (FTC)			Amprenavir (APV)
			Tipranavir (TPV)
			Atazanavir (ATV)

B First- and second-line ART regimens

First-line regimens	Stavudine + lamivudine + nevirapine d4T 30 mg + 3TC 150 mg + NVP 200 mg (all twice a day) Stavudine + lamivudine + efavirenz d4T 30 mg + 3TC 150 mg (twice a day) + EFV 600 mg (once a day) Zidovudine + lamivudine + nevirapine AZT 300 mg + 3TC 150 mg + NVP 200 mg (all twice a day) Zidovudine + lamivudine + efavirenz AZT 300 mg + 3TC 150 mg (twice a day) + EFV 600 mg (once a day)
Second-line regimens	Tenofovir + lamivudine (+ zidovudine) + lopinavir/ritonavir TDF (once a day) + 3TC (AZT) (twice a day) + LPV/RTV (twice a day) Didanosine + abacavir + lopinavir/ritonavir ddI (once a day) + ABC (once or twice a day) + LPV/RTV (twice a day)

Table 6 Early vs. late ART for co-infected patients

	Advantages	Disadvantages
Start ART early: 2–8 weeks after start of anti-tuberculosis treatment during the initial phase	• May reduce early TB-HIV morbidity and mortality, which is high in the first 2 months of anti-tuberculosis treatment • May improve sputum smear conversion rates • May be an advantage in drug-resistant TB	• High pill burden and poor drug adherence • Additive toxicities due to more anti-tuberculosis drugs in initial phase • Rifampicin-nevirapine interaction • Increased risk of immune reconstitution disease, especially if patient has a low CD4 count
Start ART later: 8 weeks after start of anti-tuberculosis treatment during the continuation phase	• Patient more stable • Pill burden less • Continuation phase may not have rifampicin, using isoniazid and ethambutol instead • Less risk of immune reconstitution disease	• 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 • Patients who get better on anti-tuberculosis treatment may not understand the additional need for ART, which might influence ART-seeking behaviour.

ART = antiretroviral treatment; TB = tuberculosis; HIV = human immunodeficiency virus.

(Table 6). Current WHO guidelines provide recommendations about when to start ART in relation to CD4 cell counts and when CD4 counts are unavailable (Table 7).[38] In practice, when CD4 cell counts are unavailable, most patients have ART delayed until the continuation phase of anti-tuberculosis treatment.

The problem with delayed initiation of ART is that many HIV-related TB deaths occur during the first 2 months of anti-tuberculosis treatment,[3] thus reducing the overall potential benefit of ART in reducing TB case fatality rates. In Malawi, where ART was provided to co-infected TB patients during the continuation phase of anti-tuberculosis treatment (i.e., after 2 months), ART had no significant impact in reducing case fatality.[43] Over 60% of deaths occurred in the first 2 months of anti-tuberculosis treatment, before ART was started, and in the continuation phase death rates were not different between those on ART and those not on ART. These results are supported by South African data, which also favour much earlier initiation of ART.[44] In particular, patients whose CD4 cell counts are <100 cells/mm^3 or who have WHO Stage 4 disease have a very high mortality risk, and should probably commence ART as soon as possible within the 2–8 week timeframe of anti-tuberculosis treatment, as recommended by the WHO.[38]

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

CD4 cell count/mm^3	ART recommendations	Timing of ART in relation to start of TB treatment
<200	Recommend ART	Between 2 and 8 weeks (in initial phase of TB treatment)†
200–350	Recommend ART	After 8 weeks (in continuation phase of TB treatment)
>350	Defer ART	Re-evaluate the patient at 8 weeks and at the end of TB treatment
Not available	Recommend ART	Between 2 and 8 weeks

* Adapted from reference 38.
† As soon as possible within this time frame for those with the most advanced immune deficiency.
ART = antiretroviral treatment; TB = tuberculosis.

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.[45] In contrast, in better resourced settings such as South Africa, early start of ART has not been overly problematic.[42] 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 8 Additive adverse drug reactions between anti-tuberculosis drugs and ART drugs

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

ART = antiretroviral treatment; ARV = antiretroviral.

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/mm^3, men with CD4 counts >400 cells/mm^3 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/mm^3 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 experience 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

Table 9 Immune reconstitution disease in TB patients starting ART

- Clinical features often include fever, lymphadenopathy, worsening respiratory symptoms and signs
- IRD usually occurs within 3 months after starting ART, but most commonly within the first 4 weeks
- Risk factors for TB-IRD include low baseline CD4 cell count, disseminated/extra-pulmonary TB, early initiation of ART and rapid immunological and virological responses to ART
- Necessary to exclude other opportunistic infections and adverse effects of drugs before making the diagnosis of IRD
- Symptoms and signs usually controlled by non-steroidal anti-inflammatory drugs or corticosteroids in more severe cases (corticosteroid dose adjusted for rifampicin interaction and tapered according to response)
- ART should be continued unless severe or life-threatening IRD develops

TB = tuberculosis; ART = antiretroviral treatment; IRD = immune reconstitution disease.

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.[58] 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.[58] However, reports from resource-poor countries to date have found lower rates of around 10%.[59] 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.[60] 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,[60] 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.[61,62] 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.[63] 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.[64] 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.[65] 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.[2] Solutions include better geographical access to ART through expansion of clinics to rural areas;[66] 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;[67] 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.[68] 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.[7] Mortality rates in patients co-infected with HIV and MDR- or XDR-TB are very high, even in specialised management programmes.[68] ART, perhaps given at an earlier stage in anti-tuberculosis treatment than is the case for drug-susceptible TB,[51,52] 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.[69] 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,[70] 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

1 Corbett E L, Watt C J, Walker N, et al. The growing burden of tuberculosis. Global trends and interactions with the HIV epidemic. Arch Intern Med 2003; 163: 1009–1021.

2 World Health Organization. Global tuberculosis control. Surveillance, planning, financing. Report 2007. WHO/HTM/TB/2005. 376. Geneva, Switzerland: WHO, 2007. http://www.who.int/tb/publications/global_report/2007/en/ Accessed February 2008.

3 Harries A D, Hargreaves N J, Kemp J, et al. Deaths from tuberculosis in sub-Saharan African countries with a high prevalence of HIV-1. Lancet 2001; 357: 1519–1523.

4 Korenromp E L, Scano F, Williams B G, Dye C, Nunn P. Effects of human immunodeficiency virus infection on recurrence of tuberculosis after rifampicin-based treatment: an analytic review. Clin Infect Dis 2003; 37: 101–112.

5 Colebunders R, Bastian I. A review of the diagnosis and treatment of smear-negative pulmonary tuberculosis. Int J Tuberc Lung Dis 2000; 4: 97–107.

6 Nunn P, Kibuga D, Gathua S, et al. Cutaneous hypersensitivity reactions due to thiacetazone in HIV-1 seropositive patients treated for tuberculosis. Lancet 1991; 337: 627–630.

7 Gandhi N R, Moll A, Sturm W, et al. Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa. Lancet 2006; 368: 1575–1580.

8 World Health Organization. Guidelines for implementing collaborative TB and HIV programme activities. WHO/HIV/2003.01.WHO/CDS/TB/2003.319. Geneva, Switzerland: WHO, 2003. http://www.who.int/tb/publications/2003/en/index1.html http://www.who.int/hiv/pub/prev_care/pub31/en/ Accessed February 2008.

9 World Health Organization. Strategic framework to decrease the burden of TB/HIV. WHO/CDS/TB/2002.296. WHO/HIV_AIDS/2002.2. Geneva, Switzerland: WHO, 2002. http://www.who.int/hiv/topics/tb/tuberculosis/en Accessed February 2008.

10 World Health Organization. Interim policy on collaborative TB/HIV activities. WHO/HTM/TB/2004. 330. WHO/HTM/HIV/2004.1. Geneva, Switzerland: WHO, 2004. http://whqlibdoc.who.int/hq/2004/WHO_HTM_TB_2004.330.pdf Accessed February 2008.

11 Harries A D, Boxshall M, Phiri S, et al. Providing HIV care for tuberculosis patients in sub-Saharan Africa. Int J Tuberc Lung Dis 2006; 10: 1306–1311.

12 De Cock K M, Odhiambo J. HIV testing in patients with TB. Trop Doct 2006; 36: 71–73.

13 Sweat M, Gregorich S, Sangiwa G, et al. Cost-effectiveness of voluntary HIV-1 counselling and testing in reducing sexual transmission of HIV-1 in Kenya and Tanzania. Lancet 2000; 356: 113–121.

14 De Cock K M, Mbori-Ngacha D, Marum E. Shadow on the continent: public health and HIV/AIDS in Africa in the 21st century. Lancet 2002; 360: 67–72.

15 World Health Organization/Joint United Nations Programme for HIV/AIDS. HIV/AIDS programme. Strengthening health services to fight HIV/AIDS. Guidance on provider-initiated HIV testing and counselling in health facilities. Geneva, Switzerland: WHO, 2007.

16 Bunnell R, Mermin J, De Cock K M. HIV prevention for a threatened continent. Implementing positive prevention in Africa. JAMA 2006; 296: 855–858.

17 Zachariah R, Spielmann M-P, Chinji C, et al. Voluntary counselling, HIV testing and adjunctive cotrimoxazole reduces mortality in tuberculosis patients in Thyolo, Malawi. AIDS 2003; 17: 1053–1061.

18 World Health Organization. The global plan to stop TB 2006–2015. Geneva, Switzerland: Stop TB Partnership, 2006. http://www.who.int/tb/features_archive/global_plan_to_stop_tb/en/index.html Accessed February 2008.

19 Zachariah R, Massaquoi M. Cotrimoxazole prophylaxis for HIV-positive TB patients in developing countries. Trop Doct 2006; 36: 79–82.

20 Wiktor S Z, Morokro M S, Grant A D, et al. Efficacy of trimethoprim-sulphamethoxazole prophylaxis to decrease morbidity and mortality in HIV-infected patients with tuberculosis in Abidjan, Cote d'Ivoire: a randomised controlled trial. Lancet 1999; 353: 1469–1474.

21 Badri M, Maartens G, Wood R, Ehrlich R. Cotrimoxazole and HIV-1 infection. Lancet 1999; 354: 334–335.

22 Joint United Nations Programme for HIV/AIDS. Provisional WHO/UNAIDS secretariat recommendations on the use of cotrimoxazole prophylaxis in adults and children living with HIV/AIDS in Africa. Geneva, Switzerland: UNAIDS, 2000. http://data.unaids.org/publications/IRC-pub04/recommendation_en.pdf Accessed February 2008.

23 Mwaungulu F B D, Floyd S, Crampin A C, et al. Cotrimoxazole prophylaxis reduces mortality in human immunodeficiency virus-positive tuberculosis patients in Karonga district, Malawi. Bull World Health Organ 2004; 82: 354–362.

24 Grimwade K, Sturm W, Nunn A J, Mbatha D, Zungu D, Gilks C F. Effectiveness of cotrimoxazole on mortality in adults with tuberculosis in rural South Africa. AIDS 2005; 19: 163–168.

25 Mermin J, Lule J, Ekwaru J P, et al. Effect of cotrimoxazole prophylaxis on morbidity, mortality, CD4-cell count, and viral load in HIV infection in rural Uganda. Lancet 2004; 364: 1428–1434.

26 Chintu C, Bhat G J, Walker A S, et al. Cotrimoxazole as prophylaxis against opportunistic infections in HIV-infected Zambian children (CHAP): a double-blind randomized placebo-controlled trial. Lancet 2004; 364: 1865–1871.

27 Zachariah R, Harries A D, Spielmann M P, et al. Changes in *Escherichia coli* resistance to cotrimoxazole in tuberculosis patients and in relation to cotrimoxazole prophylaxis in Thyolo, Malawi. Trans Roy Soc Trop Med Hyg 2002; 96: 202–204.

28 Mermin J, Lule J, Ekwaru J P, et al. Cotrimoxazole prophylaxis by HIV-infected persons in Uganda reduces morbidity and mortality among HIV-uninfected family members. AIDS 2005; 19: 1035–1042.

29 Thera M A, Sehdev P S, Coulibaly D, et al. Impact of trimethoprimsulfamethoxazole prophylaxis on falciparum malaria infection and disease. J Infect Dis 2005; 192: 1823–1829.

30 World Health Organization. Guidelines on cotrimoxazole prophylaxis for HIV-related infections among children, adolescents and adults. Recommendations for a public health approach. Geneva: Switzerland: WHO, 2006. http://www.who.int/hiv/pub/guidelines/ctx/en/index.html Accessed February 2008.
31 Mermin J, Ekwaru J P, Liechty C A, et al. Effect of cotrimoxazole prophylaxis, antiretroviral therapy and insecticide-treated bednets on the frequency of malaria in HIV-1-infected adults in Uganda: a prospective cohort study. Lancet 2006; 367: 1256–1261.
32 Lowrance D, Makombe S, Harries A, et al. Lower early mortality rates among patients receiving antiretroviral treatment at clinics offering cotrimoxazole prophylaxis in Malawi. J Acquir Immune Defic Syndr 2007; 46: 56–61.
33 Goldie S J, Yazdanpanah Y, Yosina E, et al. Cost-effectiveness of HIV treatment in resource-poor settings—the case of Cote d'Ivoire. N Engl J Med 2006; 355: 1141–1153.
34 Palella F, Delaney K, Moorman A C, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. N Engl J Med 1998; 338: 853–860.
35 Dean G L, Edwards S G, Ives N J, et al. Treatment of tuberculosis in HIV-infected persons in the era of highly active antiretroviral therapy. AIDS 2002; 16: 75–83.
36 Breen R A, Miller R F, Gorsuch T, et al. Virological response to highly active antiretroviral therapy is unaffected by antituberculosis therapy. J Infect Dis 2006; 193: 1437–1440.
37 World Health Organization/UNAIDS/UNICEF. Towards universal access. Scaling up priority HIV/AIDS interventions in the health sector. Progress report. Geneva: Switzerland: WHO, 2007. http://www.searo.who.int/LinkFiles/News_and_Events_UAPR_intro.pdf Accessed February 2008.
38 World Health Organization. Antiretroviral therapy for HIV infection in adults and adolescents: recommendations for a public health approach. Geneva: Switzerland: WHO, 2006. http://www.who.int/hiv/pub/guidelines/artadultguidelines.pdf Accessed February 2008.
39 World Health Organization. Antiretroviral therapy for HIV infection in infants and children: towards universal access. Recommendations for a public health approach. Geneva: Switzerland: WHO, 2006. http://www.who.int/hiv/pub/guidelines/art/en Accessed February 2008.
40 Centers for Disease Control and Prevention. Managing drug interactions in the treatment of HIV-related tuberculosis. Atlanta, GA, USA: CDC, 2007. http://www.cdc.gov/tb/TB_HIV_Drugs/default.htm Accessed February 2008.
41 World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis. WHO/HTM/TB/2006.361. Geneva: Switzerland. WHO, 2006. http://whqlibdoc.who.int/publications/2006/9241546956_eng.pdf Accessed February 2008.
42 Lawn S D, Myer L, Bekker L-G, Wood R. Burden of tuberculosis in an antiretroviral treatment programme in sub-Saharan Africa: impact on treatment outcomes and implications for tuberculosis control. AIDS 2006; 20: 1605–1612.
43 Zachariah R, Fitzgerald M, Massaquoi M, et al. Does antiretroviral treatment reduce case fatality among HIV-positive patients with tuberculosis in Malawi? Int J Tuberc Lung Dis 2007; 11: 848–853.
44 Lawn S D, Wood R. When should antiretroviral treatment be started in patients with HIV-associated tuberculosis in South Africa? S Afr Med J 2007; 97: 412–415.
45 van Oosterhout J J G, Kumwenda J J, Beadsworth M, et al. Nevirapine-based antiretroviral therapy started early in the course of tuberculosis treatment in adult Malawians. Antiviral Therapy 2007; 12: 515–521.
46 Breen R A, Lipman M C, Johnson M A. Increased incidence of peripheral neuropathy with co-administration of stavudine and isoniazid in HIV-infected individuals. AIDS 2000; 14: 615.
47 Stern J O, Robinson P A, Love J, Lanes S, Imperiale M S, Mayers D L. A comprehensive hepatic safety analysis of nevirapine in different populations of HIV-infected patients. J Acquir Immune Defic Syndr 2003; 34 (Suppl 1): S21–S33.
48 Sanne I, Mommeja-Marin H, Hinkle J, et al. Severe hepatotoxicity associated with nevirapine use in HIV-infected subjects. J Infect Dis 2005; 191: 825–829.
49 Teck R, Ascurra O, Gomani P, et al. WHO clinical staging of HIV infection and disease, tuberculosis and eligibility for antiretroviral treatment: relationship to CD4 lymphocyte counts. Int J Tuberc Lung Dis 2005; 9: 258–262.
50 Boulle A, Van Cutsem G, Cohen K, Hilderbrand K, Goemare E. Antiretroviral treatment outcomes in patients who received rifampicin together with nevirapine or efavirenz. 38th World Conference on Lung Health of the International Union Against Tuberculosis and Lung Disease. Cape Town, South Africa, 2007. Int J Tuberc Lung Dis 2007; 11 (Suppl): S224. [Abstract TS-71893-12]
51 Lawn S D, Edwards D J, Wood R. Concurrent drug therapy for tuberculosis and HIV infection in resource-limited settings: present status and future prospects. Future HIV Therapy 2007; 1: 387–398.
52 Swaminathan S, Luetkemeyer A, Srikantiah P, Lin R, Charlebois E, Havlir D V. Antiretroviral therapy and TB. Trop Doct 2006; 36: 73–79.
53 Ramachandran G, Hemanthkumar A K, Rajasekaran S, et al. Increasing nevirapine dose can overcome reduced bioavailability due to rifampicin coadministration. J Acquir Immune Defic Syndr 2006; 41: 1–6.
54 Manosuthi W, Kiertiburanakul S, Sungkanuparph S, et al. Efavirenz 600 mg/day versus efavirenz 800 mg/day in HIV-infected patients with tuberculosis receiving rifampicin: 48 weeks results. AIDS 2006; 20: 131–132.
55 Weiner M, Banator D, Peloquin C A, et al. Evaluation of the drug interaction between rifabutin and efavirenz in patients with HIV infection and tuberculosis. Clin Infect Dis 2005; 41: 1343–1349.
56 McIlleron H, Meintjes G, Burman W, Maartens G. Complications of antiretroviral therapy in patients with tuberculosis: drug interactions, toxicity, and immune reconstitution inflammatory syndrome. J Infect Dis 2007; 196 (Suppl 1): S63–S75.
57 Cheng V C, Ho P L, Lee R A, et al. Clinical spectrum of paradoxical deterioration during anti-tuberculosis therapy in non-HIV-infected patients. Eur J Clin Microbiol Infect Dis 2002; 21: 803–809.
58 Lawn S D, Bekker L-G, Miller R F. Immune reconstitution disease associated with mycobacterial infections in HIV-infected individuals receiving antiretrovirals. Lancet Infect Dis 2005; 5: 361–373.
59 Lawn S D, French M A. Immune reconstitution disease: recent development and implications for antiretroviral treatment in resource-limited settings. Curr Opin HIV and AIDS 2007; 2: 339–345.
60 Lawn S D, Myer L, Bekker L-G, Wood R. Tuberculosis-associated immune reconstitution disease: incidence, risk factors and impact in an antiretroviral treatment service in South Africa. AIDS 2007; 21: 335–341.
61 Fitzgerald D W, Desvarieux M, Severe P, Joseph P, Johnson W D, Pape J W. Effect of post-treatment isoniazid on prevention of recurrent tuberculosis in HIV-1-infected individuals: a randomised trial. Lancet 2000; 356: 1470–1474.
62 Churchyard G J, Fielding K, Charalambous S, et al. Efficacy of secondary isoniazid preventive therapy among HIV-infected southern Africans: time to change policy? AIDS 2003; 17: 2063–2070.
63 Lawn S D, Badri M, Wood R. Tuberculosis among HIV-infected patients receiving HAART: long term incidence and risk factors in a South African cohort. AIDS 2005; 19: 2109–2116.
64 Golub J E, Saraceni V, Cavalcante S C, et al. The impact of

antiretroviral therapy and isoniazid preventive therapy on tuberculosis incidence in HIV-infected patients in Rio de Janeiro, Brazil. AIDS 2007; 21: 1441–1448.
65 Maher D, van Gorkom J L C, Gondrie P C F M, Raviglione M. Community contribution to tuberculosis care in countries with high tuberculosis prevalence: past, present and future. Int J Tuberc Lung Dis 1999; 3: 762–768.
66 Zachariah R, Teck R, Ascurra O, et al. Can we get more HIV-positive tuberculosis patients on antiretroviral treatment in a rural district of Malawi? Int J Tuberc Lung Dis 2005; 9: 238–247.
67 Friedland G, Abdool Karim S, Abdool Karim Q, et al. Utility of tuberculosis directly observed therapy programs as sites for access to and provision of antiretroviral therapy in resource-limited countries. Clin Infect Dis 2004; 38 (Suppl): S421–S428.
68 Wells C, Cegielski P, Nelson L, et al. HIV infection and multidrug-resistant tuberculosis—the perfect storm. J Infect Dis 2007; 196 (Suppl 1): S86–S107.
69 Kang'ombe C, Harries A D, Ito K, et al. Long-term outcome in patients registered with tuberculosis in Zomba, Malawi: mortality at 7 years according to HIV status and type of TB. Int J Tuber Lung Dis 2004; 8: 829–836.
70 Corbett E L, Marston B, Churchyard G J, De Cock K M. Tuberculosis in sub-Saharan Africa: opportunities, challenges, and change in the era of antiretroviral treatment. Lancet 2006; 367: 926–937.

RÉSUMÉ

Le virus de l'immunodéficience humaine/syndrome de l'immunodéficience acquise (VIH/SIDA) et la tuberculose (TB) sont des épidémies 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 comparaison avec les patients atteints uniquement de TB. Une politique intérimaire de l'Organisation Mondiale de la Santé a été élaborée pour réduire le fardeau conjoint de la maladie VIH-TB, avec comme composante 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 traitement préventif au cotrimoxazole (CPT) et d'un traitement antirétroviral (ART). Les tests VIH sont passés d'une 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 infectés par le VIH est efficace et sûre et qu'elle constitue une part essentielle de l'ensemble des soins VIH. L'extension 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 programmatiques de la combinaison de l'ART avec le traitement antituberculeux pour atteindre le potentiel maximal de cette amélioration. Ces éléments comportent le moment optimal du début de l'ART, la meilleure façon de combiner 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 combinaison 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 humana y el síndrome de inmunodeficiencia adquirida (VIH/SIDA) y la tuberculosis (TB) provocan epidemias superpuestas que dan origen a una carga de morbilidad considerable en África subsahariana. En esta región habita la mayor cantidad de personas coinfectadas y presentan 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 morbilidad conjunta de la infección por el VIH y la TB, uno de cuyos principales componentes es la provisión de cuidados 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 pacientes tuberculosos y el suministro de tratamiento preventivo con cotrimoxazol (CPT) y de tratamiento antiretrovírico (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 eficacia y la seguridad toxicológica del CPT en pacientes infectados 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 coinfectados. Sin embargo, 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 encuentran 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 profilaxis con isoniacida con el ART tras la compleción del tratamiento antituberculoso y dónde y cómo proveer el tratamiento combinado que se acomode mejor a las necesidades del paciente. La realización de estudios clínicos y operativos en los próximos años debería ayudar a resolver algunas de estas dificultades.