

## Into the great unknown – treating drug-resistant TB and HIV

**Francesca Conradie, MB BCh, M&H, Dip HIV Man**

*Clinical Advisor for TB, Right to Care, and Deputy Director, Clinical HIV Research Unit, University of the Witwatersrand, Johannesburg*

Correspondence to: Francesca Conradie (fconradie@withealth.co.za)

Reported treatment outcomes of multidrug-resistant tuberculosis (MDR-TB) are very variable. In a large meta-analysis, including studies that used second-line drugs in individualised or standardised protocols for MDR-TB, the overall treatment success estimate, defined as the proportion of patients who were cured or completed treatment, was 62% (95% CI 58 - 67%) and 11% of the patients died. But the data on HIV status were not consistently reported.<sup>1</sup> The initial outcomes reported for extensively drug-resistant tuberculosis (XDR-TB) from the Tugela Ferry outbreak showed a very high mortality rate of 98% (52/53 cases), all of whom were HIV-infected<sup>2</sup> but in a 2009 case series of 60 XDR-TB patients 43 (72%) were HIV-positive. During follow-up 12/60 (20%) experienced sputum culture conversion, while 25/60 (42%) patients died.<sup>3</sup>

In 2011, the treatment regimens for multidrug and extensively drug-resistant tuberculosis (M/XDR-TB) in HIV non-

infected populations are based on expert opinion. The efficacy of these regimens is not based on randomised clinical trials.<sup>4</sup> Recommended regimens are lengthy and often poorly tolerated. The duration of therapy has not been established by an evidence base.

There is a significant overlap with drug-sensitive TB infection and HIV co-infection. The position is very similar in drug-resistant TB. Co-infection with HIV is in excess of 80% at many centres in South Africa. April 2010 saw the launch of a National HIV Counselling and Testing (HCT) Campaign. Health care providers must provide HIV testing to anyone diagnosed with TB. All HIV-infected patients will be regularly screened for TB symptoms. The combined initiatives will probably, in the short-term, increase the number of new cases of drug-sensitive and drug-resistant TB identified in South Africa. Finally, the revised South African Antiretroviral Treatment Guidelines of 2010 advocate initiating antiretroviral therapy (ARVs) in all HIV-infected individuals who are co-infected with drug-resistant TB as soon as possible. Thus there is an urgent need for data on treatment for the HIV co-infected MDR-TB patient.

The selection of ARV in MDR-TB patient with HIV infection has to be individualised. There are overlapping toxicities between MDR-TB treatment and ART. Tenofovir has a reported incidence of renal toxicity of 2 - 4%. Thus kanamycin, capreomycin

and amikacin, also drugs with nephrotoxic adverse events, should not be co-prescribed with tenofovir. Tenofovir should be replaced with an alternative drug for the 4 - 6-month duration of these injectable antitubercular drugs, which play an essential role in drug-resistant TB. Cycloserine or its dimer, terizidone (which is the only form currently used in South Africa) has a high incidence of neuropsychiatric adverse events. The incidence of these neuropsychiatric adverse events has not been well quantified with terizidone, but personal communications from health care workers in the field state that these reactions are common. The commonest side-effects of efavirenz (EFV), the first-line non-nucleoside reverse transcriptase inhibitor, are neuropsychiatric symptoms. These include insomnia, nightmares, dizziness, agitation, depressed mood and even overt psychosis. These adverse events of EFV occur in up to 40% of patients and are treatment limiting in 4% of patients. If patients develop intolerable neuropsychiatric symptoms when terizidone and efavirenz are co-administered, then efavirenz can be substituted with nevirapine.

Diagnostic methods for MDR-TB are rapidly changing. Until recently, the diagnosis was only made by culture, which may take up to 6 weeks to get a result as *Mycobacterium tuberculosis* is a slow-growing organism. Once a positive culture is obtained, then there is a further delay pending drug sensitivities. Molecular testing for resistance to isoniazid and rifampicin has now been

**Table I. Possible overlapping toxicities between ARV and TB treatment<sup>5</sup>**

Adverse event	Antiretroviral therapy	Antitubercular drugs	Comments
Renal toxicity	TDF (rare)	Aminoglycosides	
Central nervous	EFV	Cycloserine or terizidone, INH, ethionamide	Fluoroquinolones depersonalisation, abnormal dreams, insomnia and dizziness in the first 2 - 3 weeks, toxicity which typically resolve on their own
Depression	EFV	Cycloserine or terizidone, fluoroquinolones, INH, ethionamide	Socioeconomic circumstances of many patients can also contribute to depression
Headache	AZT, EFV	Cycloserine or terizidone	Rule out more serious causes of headache such as bacterial meningitis, cryptococcal meningitis, CNS toxoplasmosis
Peripheral neuropathy	D4T, ddI	Cycloserine or terizidone, INH, aminoglycosides, ethionamide, ethambutol linezolid	Advanced HIV disease may also contribute
Nausea and vomiting	RTV, D4T, NVP	Ethionamide, PAS, INH	
Diarrhoea	All protease inhibitors, ddI	Ethionamide, PAS, fluoroquinolones	Also consider opportunistic infections or <i>Clostridium difficile</i>
Hepatotoxicity	NVP, EFV, all protease inhibitors all NRTIs	INH, rifampicin, ethambutol pyrazinamide PAS, ethionamide, fluoroquinolones	Also consider co-trimoxazole Rule out viral of hepatitis
Abdominal pain	All ART treatment	Clofazamine, ethionamide, PAS	
Skin rash	ABC, NVP, EFV	INH, rifampicin, pyrazinamide PAS, fluoroquinolones	Do not re-challenge with ABC Also consider co-trimoxazole

introduced into routine laboratory diagnosis in South Africa, dramatically shortening the time to diagnose MDR-TB. The current molecular testing method is the Hain test, a line probe assay. However, the Hain test is a laboratory-based test which can be done directly only on smear-positive specimens or on all positive cultures. Recently a real-time PCR diagnostic test with potential as a point-of-care diagnostic test has been developed (XpertMTB). Turnaround time of this test is 1 - 2 hours and rifampicin resistance can also be detected as a marker of MDR-TB. XpertMTB has very high sensitivity for detecting rifampicin resistance, which allows for rapid initiation of treatment, but it is less specific than the Hain test and confirmation of MDR-TB by culture is still required. The XpertMTB system can be implemented in any laboratory where smear microscopy can be performed and does not require bio-safety cabinets or highly skilled technicians. There is still debate as to where this technology will be slotted in in the National TB Diagnostic Algorithm but it is likely that there will be an increase in the number of MDR-TB cases detected.

There are some new candidate drugs for the treatment of MDR-TB. The most promising and closest to registration is TMC 207, a diarylquinoline investigational compound that offers a novel mechanism of action.<sup>6</sup> While to date only HIV-negative patients or HIV-positive patients with high CD4+ counts have been included on trials, some pharmacokinetic data on interactions with antiretroviral therapies are being collected.

We are embarking on a journey into the great unknown. With the increase in HIV counselling and testing, particularly at TB clinics, the use of more rapid diagnostics methods for the diagnosis of MDR-TB, the recommendation that ART be started in an expedited fashion in HIV co-infected individuals and the lack of information on treatment interactions, there is an urgent need for research.

References available at [www.cmej.org.za](http://www.cmej.org.za)

### TB epidemiology in HIV-prevalent settings

**Keren Middelkoop, MB ChB, PhD**  
Senior Investigator and TB Division Leader,  
Desmond Tutu HIV Centre, Institute of Infectious Diseases and Molecular Medicine, University of Cape Town, and Department of Medicine, University of Cape Town

Correspondence to: K Middelkoop ([keren.middelkoop@hiv-research.org.za](mailto:keren.middelkoop@hiv-research.org.za))

The World Health Organization (WHO) estimated that in 2009 more than 9 million new cases of tuberculosis (TB) disease

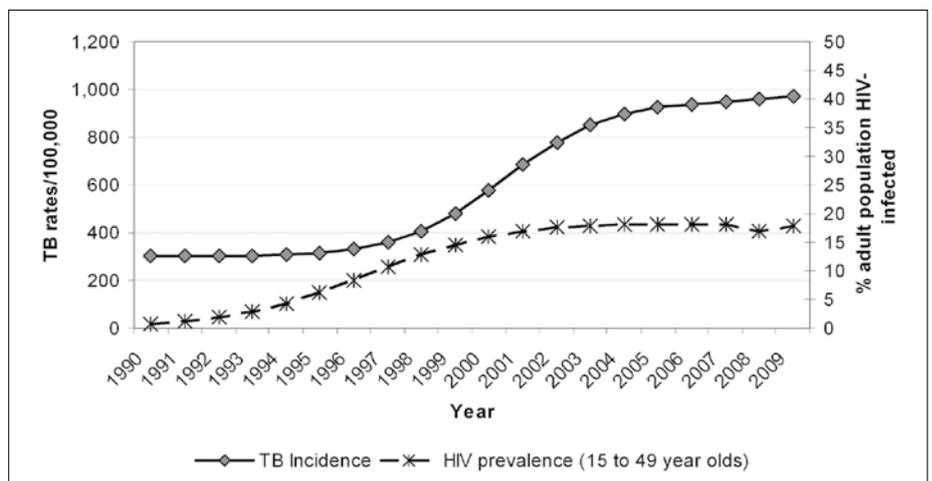


Fig. 1. TB incidence rates<sup>1,27</sup> and HIV prevalence<sup>5,28</sup> in South Africa (1990 - 2009).

occurred worldwide.<sup>1</sup> While global TB rates may be stabilising,<sup>1</sup> TB control strategies have been unable to contain TB epidemics in African countries with a high HIV prevalence.<sup>2</sup> The WHO STOP TB Partnership has proposed adjunctive strategies to address this problem, including intensified case finding, isoniazid preventive therapy, infection control measures at TB facilities<sup>3</sup> and antiretroviral therapy (ART). Of these strategies, only provision of ART has been extensively implemented.<sup>4</sup>

With over a quarter of the global burden of TB/HIV,<sup>4</sup> South Africa bears the brunt of these two epidemics. The adult HIV prevalence has risen to ~18%<sup>5</sup> in this country, while TB incidence rates have increased more than 3-fold over the past two decades<sup>1</sup> (Fig. 1). However, South Africa boasts the world's largest ART programme, with approximately 1 million patients receiving treatment.<sup>5</sup>

### Impact of HIV and ART programmes on TB disease

HIV-infected patients have a substantially increased risk of developing TB disease:<sup>6,7</sup> 10% per annum risk<sup>6</sup> versus 10% life-time risk among HIV-uninfected individuals.<sup>8</sup> Consequently, HIV is considered one of the primary factors responsible for the dramatic escalations in TB epidemics in high-prevalent settings over the past two decades.<sup>9,10</sup> It has been postulated that without the impact of the HIV epidemic, TB epidemics would be 'in decline almost everywhere'.<sup>11</sup>

It is well documented that HIV-infected patients on ART have a 61 - 90% reduction in risk of TB disease.<sup>12,13</sup> However, 2 - 3 years into treatment patients still have a 2 - 10 times higher risk of TB disease compared with HIV-uninfected individuals.<sup>14</sup> The increased longevity of HIV-infected patients on ART combined with this residual increased TB risk, has resulted in much debate on the probable impact of ART on population TB rates.

Recent studies have shown that high-coverage ART programmes are associated

with a reduction in both population TB prevalence<sup>15</sup> and notification rates,<sup>16,17</sup> and in TB-associated mortality.<sup>16</sup> This overall impact may be due to a combination of active TB case finding by means of TB screening prior to ART initiation, and the reduced risk of TB disease associated with immune recovery on ART.<sup>12,13</sup> In developing countries, ART is often initiated late in HIV disease, with the result that up to 50% of patients starting treatment have a recent history of TB and have therefore already contributed to the population TB rates.<sup>14</sup> Earlier initiation of ART may increase the beneficial impact of this intervention on population TB rates.

### Impact of HIV on TB transmission

To gain control of a TB epidemic, the incidence of infection among the younger population must be reduced.<sup>18</sup> In the 1980s there was evidence that TB infection rates among children were decreasing in developing countries,<sup>19</sup> including South Africa,<sup>20</sup> with an annual risk of TB infection (ARTI) of <2% in many African countries. However, since the advent of the HIV epidemic, the ARTI has escalated in southern Africa, reaching staggering rates of up to 4% per annum.<sup>21,22</sup>

Unfortunately, assessing the direct contribution of HIV on transmission (and the risk of TB infection) is difficult. Tests for identifying TB infection rely on immune responses to TB antigens, and HIV infection confounds this measure.<sup>23</sup> Therefore, although HIV is responsible for up to 70% of TB disease burden in high-prevalent settings, its contribution to transmission is less obvious.

While there are conflicting findings in the literature, most studies report no difference in risk of transmission from sputum-positive pulmonary TB based on the HIV status of the index case.<sup>24</sup> HIV co-infected TB patients do have higher rates of extra-pulmonary TB<sup>9</sup> and lower rates of smear-positive<sup>9,25</sup> and cavitary<sup>25</sup> TB. Overall, given the clinical characteristics of HIV-infected TB patients, it has been suggested that these patients

are responsible for approximately 7% of TB transmission in communities with a high TB prevalence.<sup>10</sup> This is supported by population-based data showing relatively stable TB rates among the HIV-uninfected population, even as rates among the HIV-infected population escalate.<sup>16,26</sup> If, indeed, HIV has only a moderate impact on TB transmission, the detection of any impact of ART programmes on transmission in communities would most likely require long-term observation in affected populations.

### Conclusion

TB remains the most common opportunistic infection and cause of death among HIV-infected patients, including those on ART.<sup>14</sup> In high TB- and HIV-prevalent settings the HIV epidemic contributes significantly to the burden of TB disease, but may be responsible for proportionally less TB transmission. High-coverage ART programmes are associated with a reduction in community TB disease burden, and a marked reduction in TB-associated mortality, reflecting both public health and individual benefit of this intervention. While the role of HIV in TB transmission appears to be relatively minor, further work is required to improve our understanding of this relationship as interventions aimed at reducing transmission are needed to gain control of this devastating epidemic.

References available at [www.cmej.org.za](http://www.cmej.org.za)

### Pharmacokinetic interactions between antiretrovirals and rifampicin-based tuberculosis treatment

**Karen Cohen, MB ChB, Assoc CCP (SA), MSc Epid (LSHTM), FCFP (SA), Dip HIV Man (SA), Dip Obst (SA)**  
Specialist, Division of Clinical Pharmacology, Groote Schuur Hospital, University of Cape Town

Correspondence to: Karen Cohen ([karen.cohen@uct.ac.za](mailto:karen.cohen@uct.ac.za))

South Africa has a huge burden of HIV and tuberculosis (TB) co-infection. Many patients are initiated on antiretroviral therapy (ART) while taking TB treatment or require TB treatment while on ART.

Rifampicin, a key component of TB treatment, is a potent inducer of drug metabolism and decreases plasma concentrations of many co-administered drugs, including non-nucleoside reverse transcriptase inhibitors, protease inhibitors and integrase inhibitors. This may result in inferior ART outcomes.

Pharmacokinetic interactions between antiretrovirals currently available in South Africa and rifampicin-based TB treatment are discussed below.

### Non-nucleoside reverse transcriptase inhibitors

Efavirenz is the non-nucleoside reverse transcriptase inhibitor of choice with rifampicin. Local data show no decrease in efavirenz concentrations in the presence of rifampicin-based TB treatment.<sup>1</sup> There is therefore no need to increase the dose of efavirenz when administered with TB treatment and the standard 600 mg daily dose should be prescribed in adults.

Nevirapine may be prescribed together with rifampicin in patients where efavirenz is contraindicated (for example during the first trimester of pregnancy, when efavirenz should be avoided because of its teratogenic potential). Nevirapine concentrations are reduced by concomitant rifampicin-containing TB treatment, and approximately 30% of patients will have sub-therapeutic nevirapine concentrations when taking standard doses of nevirapine together with TB treatment.<sup>2,3</sup> However, increasing the dose of nevirapine may result in an increased risk of hypersensitivity reactions,<sup>4</sup> and this is therefore not currently recommended as standard practice. Therapeutic drug monitoring may be useful where available, to guide nevirapine dose adjustment.

Nevirapine is usually commenced at a lead-in dose of 200 mg for the first 2 weeks, during which time auto-induction of its own metabolism takes place. Patients who are taking rifampicin already have induced hepatic enzymes. Therefore, the lead-in dose should be omitted when starting nevirapine in any patient who has been taking rifampicin-containing TB treatment for more than one week. These patients should be commenced immediately on the full nevirapine dose (200 mg 12-hourly in adults).

### Protease inhibitors

Protease inhibitors are substrates of cytochrome P450 isoenzyme 3A4 and P-glycoprotein (an efflux pump), both of which are induced by rifampicin. There is therefore a dramatic reduction in the plasma concentration of all ritonavir-boosted protease inhibitors when administered together with rifampicin-containing TB treatment.<sup>5</sup>

In order to overcome the effect of rifampicin on boosted lopinavir or saquinavir, the dose of ritonavir can be increased (400 mg of ritonavir 12-hourly in combination with 400 mg of lopinavir or saquinavir 12-hourly in adults).<sup>6,7</sup> Alternatively, for adults on boosted lopinavir, the dose of lopinavir and ritonavir can be doubled, giving a total dose of 800 mg of lopinavir 12-hourly and 200 mg of ritonavir 12-hourly.<sup>8</sup> However, doubling the dose of lopinavir and ritonavir with TB treatment should be avoided in children, as it results in sub-therapeutic lopinavir

concentrations.<sup>9</sup> Based on current data, other boosted protease inhibitors should not be prescribed with rifampicin.

Increased protease inhibitor doses may result in severe gastrointestinal side-effects, which may make adherence to treatment difficult for patients.

In studies in healthy volunteers, severe hepatotoxicity was seen when rifampicin was administered in combination with ritonavir-boosted lopinavir and saquinavir, particularly in participants initiated on rifampicin before the boosted protease inhibitor.<sup>10,11</sup> Liver functions should be monitored in all patients taking boosted lopinavir or saquinavir together with rifampicin-based TB treatment. This is particularly important when the patient is initiated on protease inhibitor therapy while taking TB treatment.

Current US guidelines recommend that rifabutin replace rifampicin in patients who require TB treatment with rifampicin concomitantly with protease inhibitor-containing ART.<sup>12</sup> However, rifabutin is very expensive and difficult to access through the South African public sector TB treatment programme. In addition it is difficult to administer within a TB programme which uses fixed-dose combination treatment.

### Nucleoside reverse transcriptase inhibitors

There are no clinically significant pharmacokinetic interactions between nucleoside reverse transcriptase inhibitors (NRTIs) and rifampicin-based TB treatment. Triple NRTI therapy is not optimal, with an increased risk of virological failure when compared with efavirenz-containing ART.<sup>13</sup> However, it may be considered in patients with TB without other treatment options (for example a public sector patient requiring TB treatment who has failed non-nucleoside reverse transcriptase inhibitor-based therapy and cannot tolerate protease inhibitor-based therapy).

### Integrase inhibitors

Raltegravir has recently become available in South Africa and is not currently available in public sector treatment programmes. In healthy volunteers, raltegravir concentrations were significantly decreased by rifampicin.<sup>14</sup> There are limited data in co-infected patients. The dose of raltegravir should be increased from 400 mg 12-hourly to 800 mg 12-hourly when co-administered with rifampicin.

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