ISSUES IN MEDICINE

When should antiretroviral treatment be started in patients with HIV-associated tuberculosis in South Africa?

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Since 1990 the HIV epidemic in South Africa has had a huge impact on the burden of tuberculosis (TB), especially within poor communities where annual notification rates have risen as high as 1 500/100 000 population.[1] Not surprisingly, as antiretroviral treatment (ART) clinics have been established in these communities, TB has emerged as a key clinical problem within these services. A large proportion of patients at programme enrolment have a history of treated TB or active TB, or develop TB during ART. For example, of patients entering a service in Gugulethu, Cape Town, 52% had a history of one or more previously treated episodes of TB, 25% had a diagnosis of active TB, and approximately 10% of patients developed TB in the first year of ART.[2]

Patients who have TB at entry to ART programmes have a high mortality risk, which is twofold greater than that of patients who do not have TB.[2] Several large studies agree that in multivariate analysis this excess mortality risk is not independently associated with TB disease activity or even with the fact that they have a TB diagnosis; instead high mortality risk is associated with these patients' degree of immunodeficiency, which is typically more advanced than that of patients who are TB free.[3-6] The fact that immunodeficiency appears to be the key determinant of mortality in these patients suggests that, in addition to antituberculosis treatment and co-trimoxazole prophylaxis, they should start ART without undue delay. However, for a long time there has been caution regarding early initiation of ART among TB patients in view of the multiple potential complications.

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Factors favouring delayed ART

The key factors thought to be important in deciding the best time to start ART in TB patients are shown in Table I. However, data from a number of studies now indicate that several of the issues favouring delayed ART are of less importance than was perhaps once thought. A major concern was that concurrent treatment would undermine ART outcomes owing to high pill burdens, poor tolerability of combined multi-drug regimens, and pharmacokinetic drug interactions. However, in Gugulethu, despite the fact that over one-third of patients have overlapping TB treatment during their first year of ART, treatment compliance levels are extremely high and over 90% of patients maintain viral load suppression rates < 400 copies/ml at all follow-up time points.[7] More specifically, TB patients receiving standard dose efavirenz-containing ART and rifampicin-containing antituberculosis treatment were found to have identical viral load suppression rates to those without TB (both 94% < 400 copies/ml at 48 weeks).[2] Data from London also confirm that ART outcomes are not undermined by concurrent antituberculosis treatment, irrespective of the timing of ART.[8] It is well established that concurrent rifampicin-containing antituberculosis treatment reduces plasma levels of non-nucleoside reverse transcriptase inhibitors (NNRTIs) by around 30%.[9,10] However, viral load suppression rates were not impaired among patients in Thailand receiving standard dosages of efavirenz-based or nevirapine-based ART at the same time as rifampicin.[9,10] All these data indicate that pharmacokinetic interactions, high pill burden and potential intolerance of combined multi-drug regimens do not undermine ART outcomes to an appreciable extent.

Another important concern is the risk of adverse events during combined treatment, especially hepatotoxicity. Many patients in sub-Saharan Africa receive nevirapine-based ART, which is well recognised to be associated with a significant risk of hepatotoxicity when used concurrently with rifampicin.[11] However, the risk of hepatotoxicity is much lower with efavirenz,[12] an alternative NNRTI which is available and widely used in South Africa. In the ART clinic in Gugulethu, where monitoring of serum hepatic transaminase concentrations is available, no deaths due to efavirenz and rifampicin co-toxicity have been observed.[6,13]

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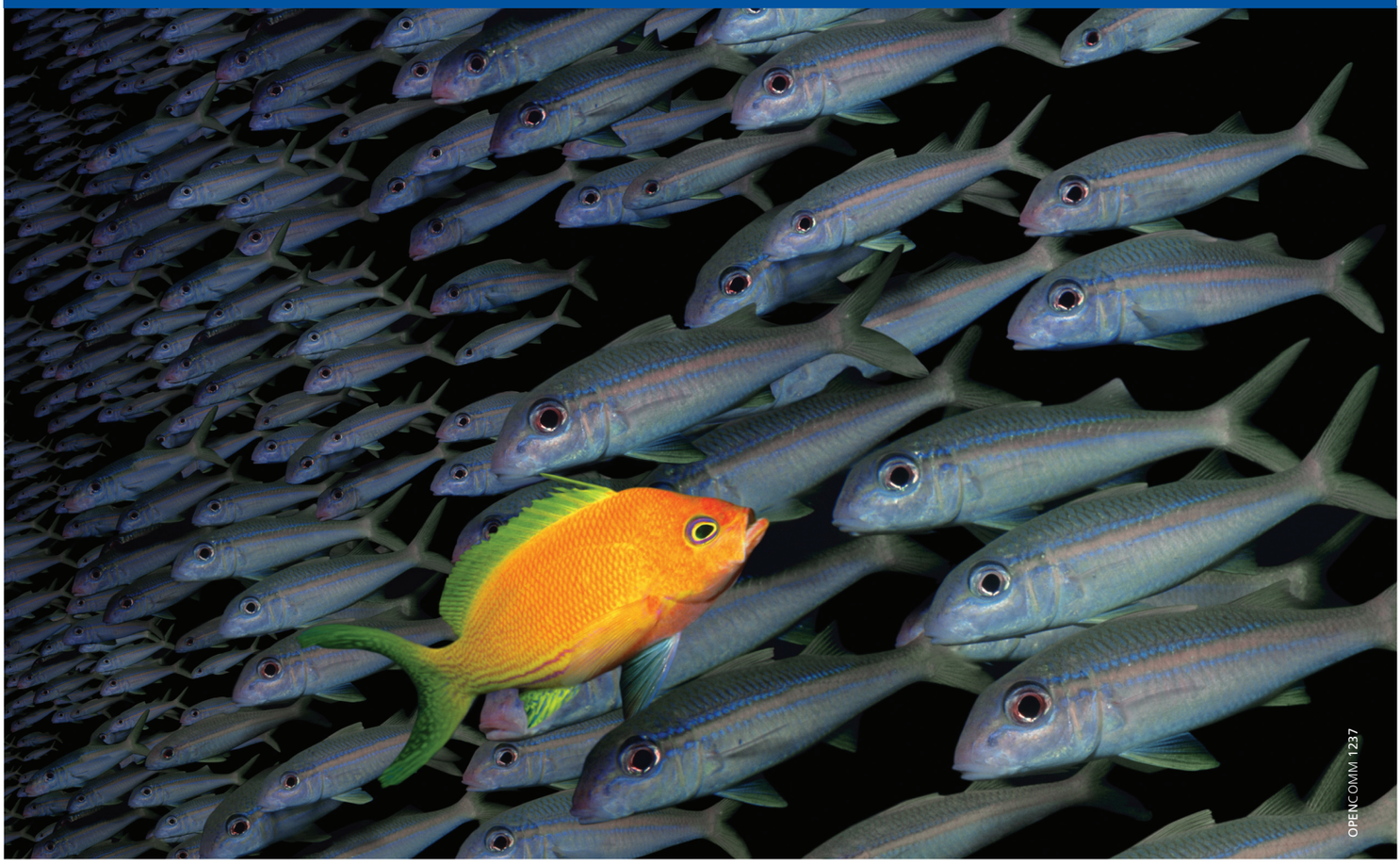

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Table I. Factors affecting the optimal time to start antiretroviral treatment (ART) in patients with tuberculosis (TB)

Factors favouring delayed initiation of ART	Potential factors favouring early initiation of ART
Pill burden and reduced adherence	Risk of further HIV-associated morbidity
Low tolerability of combined multidrug regimens	Risk of HIV-associated mortality*
Pharmacokinetic drug interactions impairing ART outcomes	Reduced risk of TB relapse
Drug co-toxicity	
Morbidity and mortality due to immune reconstitution disease*	

*Factors identified as being the most important.

Immune reconstitution disease develops in approximately 30% of patients with TB who initiate ART,[14] with the rate being highest for those with low CD4 cell counts initiating ART within the first 1 - 2 months after TB diagnosis.[14] Most cases are mild and self-limiting, but the manifestations are severe in a minority of patients and occasional deaths have been documented at the Gugulethu clinic in Cape Town and elsewhere.[15,16] Risk of mortality from immune reconstitution disease therefore remains an important variable favouring delayed initiation of ART.

Factors favouring early ART

The key argument favouring early initiation of ART in patients with TB is the risk of further HIV-associated morbidity and mortality. This risk was highlighted by observational studies from London, UK, which documented a high burden of morbidity and mortality among TB patients waiting to start ART.[17,18] However, it is important to note that early mortality rates within ART programmes in resource-limited settings are over fourfold higher than rates among patients receiving ART in high-income settings, even after adjusting for the baseline degree of immunodeficiency.[19] Consistent with this, the mortality rate among South African patients preparing to start ART is exceptionally high, with the result that even short delays in ART initiation may be associated with considerable mortality risk in this setting.[13,20] The risk assessment around timing of ART in TB patients may therefore differ between high-income and resource-limited settings and tip the balance further towards earlier ART in the latter.

Supporting this suggestion, we have analysed mortality among TB patients ($N = 73$) in the Gugulethu clinic from the time of programme enrolment until 4 months of ART. With a median delay between TB diagnosis and initiation of ART of 42 days, we found that of 14 deaths, 10 (71%) were among patients waiting to start ART and only 4 (29%) occurred during ART.[6] All patients who died awaiting ART had a CD4 cell count < 100 cells/µl or WHO stage 4 disease. While non-randomised observational data are limited, these data nevertheless suggest that currently in this clinic the number of deaths that might be averted by earlier treatment far exceeds the number of deaths that might in any way have been caused by treatment.

Antiretroviral treatment guidelines

While international guidelines agree that ART initiation can be delayed in patients with TB who have CD4 cell counts > 200 cells/µl, there is a lack of consensus regarding patients with CD4 cell counts < 200 cells/µl.[21-24] Clearly in resource-limited settings, where patients typically access ART services with very advanced immunodeficiency, this must be a mortality-based decision. In the situation where an efavirenz-based (low hepatotoxicity risk) ART regimen is used, we agree with workers elsewhere[25] that the decision analysis in South Africa centres around two key issues: the mortality risk associated with delayed ART versus the mortality risk from immune reconstitution disease with early ART. Currently, pre-ART deaths in the Gugulethu clinic greatly exceed those that occur during treatment, indicating the potential for mortality reduction from earlier treatment.

The current *South African Antiretroviral Treatment Guidelines* (1st edition)[26] state that ART should be delayed for 2 months except for patients with a CD4 cell count < 50 cells/µl or a 'serious HIV illness'. However, the data we have reviewed in this article clearly suggest that these should be revised. The current WHO antiretroviral treatment guidelines (2006) state that for patients with TB and a CD4 cell count < 200 cells/µl ART should be started between 2 and 8 weeks of TB treatment and that for those with severe immunosuppression ART should be started as soon as possible within this time-frame once antituberculosis treatment is tolerated. The data we have reviewed from South Africa strongly support these guidelines and a move towards earlier treatment, especially for patients with CD4 cell counts < 100 cells/µl or stage 4 disease.

Integration of TB and HIV clinical services

In addition to changes in treatment guidelines, much needs to be done to foster closer working relationships between TB clinics and ART services. Fifteen per cent of patients entering the ART clinic in Gugulethu have had TB diagnosed elsewhere prior to referral for ART.[2] These patients arrive at the ART clinic having already completed a median of 3 months of antituberculosis treatment despite having a median CD4 cell count of just 66 cells/µl.[6] This represents a huge delay and it is very likely that considerable mortality occurs among such patients before

they reach the ART programme. HIV status and blood CD4 cell counts should be promptly assessed at TB diagnosis and, where appropriate, patients should be quickly referred to the ART service. However, in Gugulethu, for example, these separate clinics are over a mile apart and are run separately by provincial and city administrations. This clearly highlights the need for close collaboration or integration of TB treatment and ART services.

Conclusions

The new HIV/AIDS and sexually transmitted infections (STI) Strategic Plan for South Africa 2007 - 2011 offers new hope for the millions of South Africans who are living with HIV and sets important targets to improve joint management of TB and HIV. To enable our clinical services to provide better care for those with both diseases, we also suggest that the South African national antiretroviral treatment guidelines for use of ART in patients with TB should be updated to recommend earlier initiation of treatment. Moreover, stronger efforts should be made towards greater integration of TB and HIV treatment services.

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