# USING ANTIRETROVIRAL THERAPY IN PATIENTS WITH TUBERCULOSIS

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Tuberculosis is the commonest cause of morbidity and mortality in HIV-infected patients in sub-Saharan Africa. With increasing access to antiretroviral therapy in the region, it is inevitable that large numbers of patients will either develop tuberculosis while on antiretroviral therapy or be considered for antiretroviral therapy when tuberculosis develops. There are complex drug interactions and shared toxicity of antiretroviral and tuberculosis therapy that need to be considered. Furthermore, antiretroviral therapy can lead to paradoxical deterioration of tuberculosis. This article reviews these complex interactions and provides recommendations for using antiretroviral and tuberculosis therapy in the southern African context.

## SHARED TOXICITY

Shared or overlapping toxicity is common and leads to difficult management decisions if the toxicity warrants stopping therapy. The commonest shared toxicities are peripheral neuropathy, nausea, rash and hepatitis. Peripheral neuropathy due to isoniazid can be prevented with pyridoxine, and it is prudent to give this to all HIV-infected patients even if they are not on antiretroviral therapy, as peripheral neuropathy is commonly due to HIV. Drugs that are likely to be responsible are listed in Table I.

## DRUG INTERACTIONS

This is discussed fully in the next issue in an article by Cohen *et al.* The problem is that rifampicin is a powerful enzyme inducer that leads to enhanced metabolism of protease inhibitors (except ritonavir) and, to a lesser extent, non-nucleoside reverse transcriptase inhibitors. Rifampicin levels are not significantly affected by antiretroviral therapy. Antiretroviral drugs that can be used concomitantly with rifampicin are listed in Table II.

Suitable antiretroviral regimens for patients on rifampicin therefore include:

- Triple nucleoside RTI (effective provided the viral load is < 50 000 copies/ml or < 100 000 copies/ml if abacavir is used)
- Dual nucleoside RTI plus efavirenz
- Dual nucleoside RTI plus ritonavir (or ritonavir plus saquinavir).

Rifabutin is a less potent enzyme inducer than rifampicin, and certain protease inhibitors affect its levels. Rifabutin can be used as an alternative to rifampicin in the treatment of tuberculosis and is recommended as an alternative to rifampicin in industrialised countries, but it is expensive and not available at southern African state clinics where tuberculosis is treated. For this reason it is not considered further in this article.

**TABLE I. COMMON SHARED TOXICITY OF ANTIRETROVIRAL AND ANTITUBERCULOSIS THERAPY**

| Toxicity | Antituberculosis therapy | Antiretroviral therapy |
|---|---|---|
| Peripheral neuropathy | Isoniazid | Stavudine<br>Zalcitabine<br>Didanosine |
| Rash | Rifampicin<br>Isoniazid<br>Pyrazinamide | Non-nucleoside RTI |
| Nausea | Pyrazinamide | Didanosine<br>Zidovudine<br>Protease inhibitors |
| Hepatitis | Rifampicin<br>Isoniazid<br>Pyrazinamide | Non-nucleoside RTI |

RTI - reverse transcriptase inhibitor.

| TABLE II. DRUG INTERACTIONS BETWEEN RIFAMPICIN AND ANTIRETROVIRAL THERAPY | |
|---|---|
| Nucleoside RTI | No interactions |
| Efavirenz | Mild reduction in efavirenz levels – some experts increase the dose to 800 mg |
| Nevirapine | Moderate reduction in nevirapine levels – limited experience |
| Ritonavir (full dose) | No significant interaction |
| Ritonavir + saquinavir (both 400 mg b.d.) | No significant interaction |
| All other protease inhibitors | Marked reduction in protease inhibitor levels – avoid |

## PARADOXICAL WORSENING OF TUBERCULOSIS

Paradoxical deterioration of tuberculosis despite effective antituberculosis therapy was well documented in the pre-HIV era. Typical cases observed were enlargement of lymph nodes or tuberculomas. Paradoxical reactions occur far more commonly in HIV-infected patients and include worsening or new pulmonary infiltrates. In most case series the paradoxical reactions are temporally related to the initiation of antiretroviral therapy (especially when this is commenced within the first 2 months of antituberculosis therapy), occurring in about a third of patients.

The mechanism of the paradoxical reactions is believed to be due to the host immune response – either because of increased antigen release following antituberculosis therapy or because of immune reconstitution from antiretroviral therapy. The latter is known as immune restoration syndrome and typically occurs in patients who initiate highly active antiretroviral therapy with low CD4+ lymphocyte counts. The other pathogens that are frequently associated with immune restoration syndromes are cytomegalovirus and *Mycobacterium avium* complex.

## TREATING TUBERCULOSIS DEVELOPING ON ANTIRETROVIRAL THERAPY

Rifampicin-based short-course therapy is well studied and highly effective in treating HIV-associated tuberculosis. There are limited data on treating tuberculosis in HIV-infected patients without using rifamycins. Regimens containing streptomycin appear to be best, but the duration of therapy is uncertain and the toxicity is considerable. When patients develop tuberculosis while on antiretroviral therapy it is therefore extremely important to try to switch the patient to an antiretroviral regimen that can be used with rifampicin. In most instances a switch is possible. If this is not possible, the sensitivity of the organism should be checked. Therapy should be commenced (while awaiting the sensitivity results) with isoniazid, pyrazinamide, ethambutol and streptomycin – the latter can be given 3 times a week. The duration of therapy should be at least 9 months. Streptomycin should be continued for as long as tolerated and regular audiograms should be done to check for ototoxicity, which is often irreversible.

## STARTING ANTIRETROVIRAL THERAPY WITH NEWLY DIAGNOSED TUBERCULOSIS

In areas where tuberculosis is endemic, like southern Africa, HIV-infected patients develop tuberculosis with a wide range of immune suppression. Tuberculosis *per se* should therefore not be considered a criterion for starting antiretroviral therapy. Because of the problems of paradoxical reactions, drug interactions and shared toxicity discussed above, antiretroviral therapy should not be commenced at the same time as antituberculosis therapy. Deciding when to start antiretroviral therapy depends on the CD4+ lymphocyte count and other serious HIV-related co-morbidity:

- **CD4 > 200 cells/µl.** Defer antiretroviral therapy until after antituberculosis therapy. As CD4 counts tend to increase when tuberculosis is treated, these should be repeated after antituberculosis therapy to see if the patient needs antiretroviral therapy.
- **CD4 50 - 200 cells/µl.** Defer antiretroviral therapy until after the intensive phase (2 months) of antituberculosis therapy. At this stage the number of antituberculosis drugs is reduced, with less chance of shared toxicity, and the risk of paradoxical reactions is lower.
- **Serious HIV-related co-morbidity or CD4 < 50 cells/µl.** Start antiretroviral therapy once it is clear that the patient is tolerating antituberculosis therapy. This will generally be after about 2 weeks.


RECOMMENDED READING

Dean GL, Edwards SG, Ives NJ, *et al.* Treatment of tuberculosis in HIV-infected persons in the era of highly active antiretroviral therapy. *AIDS* 2002; **16:** 75-83.

Burman WJ, Jones BE. Treatment of HIV-related tuberculosis in the era of highly effective antiretroviral therapy. *Am J Respir Crit Care Med* 2001; **164:** 7-12.

Centers for Disease Control. Updated guidelines for the use of rifabutin or rifampin for the treatment and prevention of tuberculosis among HIV-infected patients taking protease inhibitors or nonnucleoside reverse transcriptase inhibitors. *Morb Mortal Wkly Rep* 2000; **49:** 185-189.