

MANAGEMENT OF HIV AND TUBERCULOSIS CO-INFECTION IN SOUTH AFRICA

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Many HIV-infected patients in South Africa are co-infected with tuberculosis, and tuberculosis is the leading cause of morbidity and mortality in HIV-infected South Africans.¹ From the time of HIV infection, the individual's susceptibility to tuberculosis is increased, and as the HIV epidemic in South Africa progresses, the incidence of new cases of tuberculosis continues to increase.

Antiretroviral (ARV) access in South Africa is expanding, with the implementation of a governmental comprehensive HIV policy in the public sector which includes access to ARV therapy. ARV therapy has been shown to reduce the incidence of tuberculosis in HIV-infected patients by more than 80% in a study in Cape Town,¹ but because of the high background incidence of tuberculosis, a substantial number of patients will still present with active tuberculosis while on ARV therapy. In addition, many patients being worked up for ARV therapy initiation are found to have active tuberculosis.

This article discusses management of HIV-infected patients with tuberculosis in South Africa. Clinically significant drug interactions between standard, rifampicin-based therapy and the first- and second-line ARV regimens of the South African national ARV treatment protocol² are discussed, as well as implications of co-administration of ARVs and antituberculosis therapy for treatment adherence. Timing of initiation of ARV therapy in an HIV-infected patient presenting with tuberculosis is considered. Areas for further research are outlined.

DRUG METABOLISM INTERACTIONS (PHARMACOKINETIC INTERACTIONS)

Clinically significant pharmacokinetic drug interactions exist between standard tuberculosis treatment and ARV therapy. The rifamycin rifampicin is a potent inducer of the cytochrome P450 enzyme system, particularly the dominant iso-enzyme CYP3A4. Rifampicin therefore increases metabolism and reduces plasma levels of many hepatically metabolised drugs, including non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs). Decreased plasma levels may result in ARV treatment failure.

Rifampicin is a critical component of tuberculosis treatment. HIV-infected patients treated with rifamycin-sparing regimens require protracted streptomycin-based treatment, with treatment duration of 9 - 12 months to prevent relapse. The Centers for Disease Control and Prevention (CDC) have recently released updated guidelines for the treatment of tuberculosis in HIV-infected patients (reprinted in the previous edition of this journal³). Their recommendations include using rifabutin instead of

rifampicin for patients taking PIs or NNRTIs, as rifabutin is a far weaker enzyme inducer than rifampicin. However, rifabutin is extremely expensive and is not available within the South African tuberculosis control programme. All cases of tuberculosis should be managed by the tuberculosis control programme, so it is therefore recommended that the ARV regimen be modified to make it compatible with standard, rifampicin-based tuberculosis treatment. Rifampicin doses do not need to be adjusted when combined with ARV therapy (in contrast to rifabutin, where levels are increased by PIs).

NNRTI levels are reduced when co-administered with rifampicin. The area under the curve (a standard measure of drug concentration) of efavirenz is reduced by 22% and nevirapine by 37 - 58%.³ Trough levels (the pharmacokinetic parameter that correlates best with virological response) of efavirenz and nevirapine remain therapeutic, although they are also reduced. The CDC recommends increasing the efavirenz dose to 800 mg daily in order to overcome the enhanced metabolism induced by rifampicin.³ However, a population pharmacokinetic study of efavirenz showed that hepatic clearance was 28% higher

in white non-Hispanics than in African Americans and Hispanics.⁴ Major ethnic differences exist in allelic variations of iso-enzyme CYP2B6, which is primarily responsible for metabolising efavirenz.⁵ There are no published data on efavirenz metabolism in the South African population. Because of concerns about increased toxicity, increasing the efavirenz dose when co-administered with rifampicin is not recommended in the South African guidelines. Nevirapine clearance may also vary between ethnic groups owing to genetic variability in drug metabolism.⁶ There is reasonable clinical evidence that standard doses of nevirapine are effective when co-administered with rifampicin.³

Most PI levels are dramatically reduced when co-administered with rifampicin and must not be used, except ritonavir, which is a powerful inhibitor capable of overcoming the induction provided doses of 400 mg twice daily or more are used (e.g. the dual combination of ritonavir 400 mg plus saquinavir 400 mg twice daily OR lopinavir/ritonavir (Kaletra) 3 tablets plus additional ritonavir 300 mg twice daily). Ritonavir causes gastrointestinal intolerance in many patients. Gradual dose escalation of the ritonavir dose over a period of 1 week helps improve tolerability.

ARV therapy consisting of three nucleoside reverse transcriptase inhibitors (NRTIs) was previously recommended by the CDC as there are no significant interactions between rifampicin and NRTIs. However, recent studies clearly show these regimens are inferior to conventional highly active antiretroviral therapy (HAART) and triple NRTI regimens are no longer recommended.³

Table I gives NNRTI and PI recommendations for use with rifampicin in the South African context.

ADDITIVE SIDE-EFFECTS (PHARMACODYNAMIC INTERACTIONS)

There is an additive risk of side-effects and drug toxicity when ARVs and drugs used for treatment of tuberculosis are administered together (Fig. 1). Pyridoxine should be given to all HIV-infected patients taking tuberculosis treatment, to reduce the risk of isoniazid-induced peripheral neuropathy. Patients who drink alcohol excessively are at increased risk of hepatotoxicity and peripheral neuropathy, and should be counselled to decrease their alcohol intake. Shared side-effects and toxicities are summarised in Table II.

TABLE II. COMMON CAUSES OF SHARED SIDE-EFFECTS OF ANTITUBERCULOSIS AND ARV THERAPY

| Side-effect | ARV | Antituberculosis drug |
|-----------------------|-----------------------------------|---|
| Nausea | Didanosine, zidovudine, ritonavir | Pyrazinamide |
| Hepatitis | Nevirapine, efavirenz | Rifampicin, isoniazid, pyrazinamide |
| Peripheral neuropathy | Stavudine, didanosine | Isoniazid |
| Rash | Nevirapine, efavirenz | Rifampicin, isoniazid, pyrazinamide, ethambutol |

TABLE I. SOUTH AFRICAN RECOMMENDATIONS FOR CO-ADMINISTERING PIs AND NNRTIs WITH RIFAMPICIN

| Single PIs | Recommended dose when combined with rifampicin | Comments |
|--|--|---|
| Ritonavir | 600 mg 12-hourly | Ritonavir is poorly tolerated in adults because of gastro-intestinal side-effects, and is therefore not commonly used as a single PI |
| Amprenavir Indinavir Nelfinavir Saquinavir | Rifampicin should not be used together with these single PIs | Change the regimen to make it compatible with rifampicin, taking the patient's previous ARV therapy into account (do not use a drug that the patient has previously failed) |
| Boosted PI combinations | | |
| Saquinavir/ritonavir | Saquinavir 400 mg + ritonavir 400 mg 12-hourly | Limited clinical experience |
| Lopinavir/ritonavir | Lopinavir/ritonavir (Kaletra) 400 mg/100 mg + ritonavir 300 mg 12-hourly | Limited clinical experience |
| Non-nucleoside reverse transcriptase inhibitors | | |
| Efavirenz | 600 mg/d | CDC guidelines recommend 800 mg, but efavirenz metabolism is slower in African Americans and increased central nervous system side-effects may occur with the 800 mg dose |
| Nevirapine | 200 mg twice daily | Possible increased risk of hepatotoxicity, particularly during the first 2 months of nevirapine-containing ARV therapy |



Fig. 1. Hypersensitivity skin rashes in HIV-infected patients treated for tuberculosis and HIV can be due to antituberculosis therapy, co-trimoxazole or non-nucleoside reverse transcriptase inhibitors.

MANAGEMENT OF HIV-INFECTED PATIENTS DIAGNOSED WITH ACTIVE TUBERCULOSIS WHEN TAKING ARV THERAPY ACCORDING TO NATIONAL GUIDELINES

If a patient who is already on ARV therapy develops tuberculosis, ARV therapy should be continued throughout standard tuberculosis treatment, with changes, where necessary, to his/her treatment regimen.

The recommended first-line treatment regimen for ARV-naïve patients in the public sector is the following:

1. Stavudine (d4T) 40 mg every 12 hours (or 30 mg every 12 hours if < 60 kg), plus
2. Lamivudine (3TC) 150 mg every 12 hours, plus
3. Either efavirenz (EFV) 600 mg at night (or 400 mg if < 40 kg) or nevirapine (NVP) 200 mg daily for 2 weeks, followed by 200 mg every 12 hours. As efavirenz is teratogenic, women of childbearing potential who want to fall pregnant, or who are unwilling to use injectable hormonal contraception, are treated with nevirapine.

Patients who develop tuberculosis while taking efavirenz-based first-line therapy should continue their ARV therapy unchanged throughout tuberculosis treatment. If patients are stable (preferably ≥ 2 months) on nevirapine when

tuberculosis develops, the regimen can be continued. Some prefer to change from nevirapine to efavirenz because the interaction between efavirenz and rifampicin is less marked. Patients treated with concomitant nevirapine and rifampicin should be carefully monitored for hepatotoxicity, and transaminases should be monitored monthly.

Patients who fail the first-line treatment regimen will be commenced on PI-based second-line ARV therapy as follows:

1. Didanosine (ddl) 400 mg once a day (250 mg daily if < 60 kg), plus
2. Zidovudine (AZT) 300 mg every 12 hours, plus
3. Lopinavir/ritonavir (LPV/r) 400/100 mg every 12 hours.

If tuberculosis is diagnosed in a patient taking the above treatment regimen, ritonavir 300 mg twice daily should be added to the regimen (to give a total dose of lopinavir 400 mg twice daily and ritonavir 400 mg twice daily). When rifampicin is stopped, it takes about 2 weeks before cytochrome P450 iso-enzyme induction is reversed. Therefore, the added ritonavir should only be stopped 2 weeks after completion of tuberculosis treatment.

MANAGEMENT OF HIV-INFECTED PATIENTS DIAGNOSED WITH ACTIVE TUBERCULOSIS AND NOT YET TAKING ARV THERAPY

It is estimated that more than half of new adult cases of tuberculosis in South Africa are co-infected with HIV. The majority of these patients are not taking ARV therapy, and many of them do not yet fulfil clinical criteria for ARV therapy initiation. Clinical criteria for initiation of ARV therapy in the public sector in South Africa are as follows: The patients must have World Health Organisation (WHO) stage 4 disease (AIDS) or a CD4 count of less than 200 cells/ μ l. Extrapulmonary tuberculosis, although it is a WHO stage 4 defining illness, is not a criterion for initiating ARV therapy unless the CD4 count is less than 200 cells/ μ l.

If the patient has no history of WHO stage 4 illness, and has a CD4 count of more than 200 cells/ μ l, ARV therapy is not clinically indicated. The need for antiretrovirals should be reassessed on completion of tuberculosis treatment.

If the patient has a history of WHO stage 4 illness and/or a CD4 count of less than 200 cells/ μ l, ARV therapy is indicated. However because of the risk of additive side-effects and drug toxicity, it is preferable to complete 2 months of tuberculosis therapy before commencing ARVs. If the patient has a CD4 count of less than 50 cells/ μ l or other serious HIV-related illness, ARV therapy can be commenced earlier, from 2 weeks. In this setting ensure that the patient is tolerating tuberculosis treatment and responding to it before initiating ARV therapy. However, it

is difficult to establish patient readiness for HAART within 2 weeks. Patients in the public sector should be started on first-line therapy consisting of stavudine, lamivudine and efavirenz. Initiation of nevirapine during tuberculosis treatment should generally be avoided because of limited evidence and danger of shared hepatotoxicity.

Multidrug-resistant (MDR) tuberculosis has a poor prognosis in HIV-infected patients. All HIV-infected patients with MDR tuberculosis should therefore be considered for ARV therapy, even if their CD4 count is above 200 cells/ μ l. These patients may have a previous history of poor adherence to TB therapy, and should only be considered for ARV therapy if causes of poor adherence (e.g. substance abuse) have been adequately dealt with. They require intensive adherence support. There are shared side-effects and potential drug interactions between ARVs and drugs used to treat MDR tuberculosis, which will be discussed in a separate article.

ADHERENCE

Patients taking concomitant ARV and antituberculosis treatment are required to take a large number of tablets every day. They are likely to develop side-effects such as gastro-intestinal intolerance, which may make adherence to treatment difficult. These patients require intensive adherence support. Adherence tools such as pill boxes may be helpful. Side-effects that impact on adherence, e.g. nausea, should be actively managed. If a patient cannot tolerate the side-effects or pill burden, an ARV treatment interruption for the duration of tuberculosis treatment may be considered.

IMMUNE RECONSTITUTION

Patients with advanced HIV disease, particularly those with a CD4 count of less than 50 cells/ μ l, may become ill with an immune reconstitution illness during the first few months of ARV therapy. In this setting improving immune function may cause paradoxical deterioration of an opportunistic infection being treated or unmask a previously occult opportunistic infection. In South Africa, patients with advanced HIV infection and tuberculosis co-infection commonly develop immune reconstitution illness when ART is commenced. In many instances the paradoxical

deterioration of tuberculosis is mild, but it can occasionally be life-threatening. Patients may present with fever, lymphadenopathy or worsening pulmonary infiltrates. Immune reconstitution illness is not indicative of drug failure or a drug side-effect. It is not a reason to stop ARV therapy, or to change the ARV regimen. The role of corticosteroids in the management of patients with immune reconstitution tuberculosis is unclear at present, but should be considered for severe reactions.

AREAS FOR FUTURE RESEARCH

Current knowledge of ARV interactions with anti-tuberculosis therapy is often based on individual case reports and small studies. There is evidence suggesting genetic variability in the metabolism of the NNRTIs nevirapine and efavirenz, the clinical significance of which is currently unclear.^{4,6} Larger studies, involving southern African patients, are needed to guide local clinical practice and local dosing recommendations. There are few published data on ARV levels in children treated for tuberculosis. Recommendations for treatment of children are currently based on extrapolation from limited data in adults, and there is an urgent need for paediatric studies. Therapeutic monitoring of ARV drug levels and individual dosing in patients being treated for tuberculosis is logical, but clinical benefit needs to be demonstrated in a study. The optimal timing of initiating ARV therapy in patients with tuberculosis can only be addressed in a randomised controlled trial. There is a need for pharmaco-epidemiological studies to assess the frequency and severity of shared side-effects.

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