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Tuberculosis and HIV Co-Infection

A Practical Therapeutic Approach

Ronan A.M. Breen, *Leonie Swaden*, *Jayne Ballinger* and *Marc C.I. Lipman*

Department of HIV Medicine, Royal Free Hospital, London, England

Contents

Abstract

HIV and tuberculosis (TB) are leading global causes of mortality and morbidity, and yet effective treatment exists for both conditions. Rifamycin-based antituberculosis therapy can cure HIV-related TB and, where available, the introduction of highly active antiretroviral therapy (HAART) has markedly reduced the incidence of AIDS and death. Optimal treatment regimens for HIV/TB co-infection are not yet clearly defined. Combinations are limited by alterations in the activity of the hepatic cytochrome P450 (CYP) enzyme system, which in particular may produce subtherapeutic plasma concentrations of antiretroviral drugs. For example, protease inhibitors often must be avoided if the potent CYP inducer rifampicin is co-administered. However, an alternative rifamycin, rifabutin, which has similar efficacy to rifampicin, can be used with appropriate dose reduction. Available clinical data suggest that, for the majority of individuals, rifampicin-based regimens can be successfully combined with the non-nucleoside reverse transcriptase inhibitors nevirapine and efavirenz. Most available HAART regimens in areas that have a high burden of TB contain one or the other of these drugs as a backbone. However, significant questions remain as to the optimal dose of either agent required to ensure therapeutic plasma concentrations, especially in relation to particular ethnic groups. The timing of HAART initiation after starting antituberculosis therapy continues to be controversial. Debate centres upon whether early initiation of HAART increases the risk of paradoxical reactions (immune reconstitution-related events) and other adverse events, or whether delay greatly elevates the risk of disease progression. Further prospective clinical data are needed to help inform practice in this area.

Tuberculosis (TB) and HIV are inextricably linked. Globally, they are leading causes of mortality and morbidity.[1] Effective drug therapy exists which can cure TB; whilst highly active antiretroviral therapy (HAART) has had a dramatic effect in reducing the occurrence of AIDS and death, and

improving the health status of individuals infected with HIV.[2,3] Thus, the outlook for individuals diagnosed with HIV/TB co-infection is good if such treatments are available and can be combined successfully. In this review, we discuss the practical, clinical issues we believe to be important in this vibrant area of therapeutics. We have used peer-reviewed published data, and have sought to highlight where we believe there remains a lack of an adequate evidence-base for clinical practice.

1. Treatment of Tuberculosis (TB) in HIV Infected Individuals

Since the beginning of the HIV epidemic, co-infection with TB has been a major cause of AIDS and death.[4] It became apparent that the progression of HIV-related immune suppression greatly increased the risk of reactivation of latent TB and the development of progressive primary disease in recently infected individuals.[5,6] However, despite this and the risk of developing further AIDS-related illnesses, data have clearly shown that even before the introduction of HAART, it was possible to achieve good TB outcomes in individuals able to tolerate and adhere to effective antituberculosis therapy.[7,8]

Effective antituberculosis regimens were developed long before the discovery of HIV through a series of well controlled studies in large numbers of patients. These have established that in the majority of patients, rapid sterilisation and ultimately cure can be achieved by the combined use of rifampicin and isoniazid for 6 months with the addition of pyrazinamide, and ethambutol or streptomycin if significant risk of drug resistance exists, for the initial 2 months.[9] Interestingly, this appears to be true despite a number of studies that have demonstrated an association between HIV infection and low serum concentrations of rifampicin, ethambutol and isoniazid.[10-12] Such a regimen is now the basis for global treatment efforts often employing fixed-dose combinations.[13] This has largely eliminated the use of cheaper but less effective non rifamycin-based regimens, often containing thioacetazone (thiacetazone). These cheaper drugs needed to be taken for longer, and were associated with a significantly greater frequency of adverse events, especially for those with HIV co-infection.[14]

The hepatic cytochrome P450 (CYP) enzyme system plays an important role in the metabolism of rifamycins, and the protease inhibitor (PI) and non-nucleoside reverse transcriptase inhibitor (NNRTI) antiretroviral agents. Most HAART regimens contain at least one drug from either of the latter two classes and so combining a rifamycin with HAART may cause drug-drug interactions.[15] Rifampicin is a potent inducer of CYP enzymes that may be problematic when combined with NNRTIs and especially PIs. Rifabutin is an alternative rifamycin with a less marked effect on CYP. In comparison to the large body of outcome data for the use of rifampicin in treating TB, that supporting the role of rifabutin is less extensive; however, what has been reported to date suggests that it produces equivalent outcomes to rifampicin with similar tolerability in both those infected and those not infected with HIV.[16-19] Where it does appear less efficacious is when used in more intermittently administered regimens. Here, it appears to be associated with a significant risk of treatment failure and TB relapse, often with the development of acquired rifamycin resistance. This seems to be predominantly in individuals with low blood CD4+ cell counts.[20] Similar results were reported when the long-acting rifamycin, rifapentine, was used in an intermittent regimen in HIV-infected individuals.[21]

Currently, other commonly used antituberculosis agents appear not to significantly interact with antiretrovirals. There has been an increased effort in recent years to identify new, effective antituberculosis agents that may decrease treatment duration and it will be important to carefully evaluate these for drug-drug interactions and overlapping toxicity when used with antiretrovirals. Although not new, data from animal treatment models and human studies of early bactericidal activity in sputum have suggested that the fluoroquinolones may be potentially important antituberculosis drugs.[22,23] However, it is important to note that in some countries these drugs are widely used to treat communi-

ty-acquired pneumonia with the potential for partial treatment of unsuspected TB and consequent delay in initiation of appropriate therapy and the generation of quinolone-resistant TB.[24-26] Presently, moxifloxacin has been shown to be equivalent to ethambutol when used with rifampicin, isoniazid and pyrazinamide in the first 2 months of therapy for pulmonary TB in a cohort of patients of whom 22% were HIV infected.[27] Further large-scale clinical studies will be required to evaluate the utility and cost of regimens containing fluoroquinolones in comparison with current standard drugs.

2. Use of Highly Active Antiretroviral Therapy (HAART) in HIV Infected Individuals with TB

Most guidelines suggest that HAART should be started in individuals with blood CD4+ cell counts between 200 and 350 cells/μL, irrespective of symptoms or other illnesses.[28,29] This recognises that the risk of progression to AIDS increases substantially below a CD4+ cell count of 200 cells/μL. Unlike the majority of severe HIV-related illness, active TB can occur in both immunosuppressed and immunocompetent individuals.[30] Therefore, its presence should not be regarded as an absolute indication to start HAART in HIV co-infected individuals. Where reliable CD4+ cell count measurements are available, these, as well as the overall clinical scenario, can guide such decisions.[31,32] However, many patients with HIV/TB co-infection will have blood CD4+ cell counts low enough to consider starting HAART anyway. For example, a study from Malawi demonstrated that 90% of 457 individuals with active or previous TB presenting to an antiretroviral clinic had a CD4+ cell count <350 cells/μL. The investigators inferred from this that where CD4+ cell counts are not routinely available, a history of previous or current TB is a good enough reason to offer antiretrovirals.[33]

A number of potential problems can be encountered if HAART and antituberculosis therapy are prescribed concurrently. These include overlapping toxicities, increased pill burden and risk of suboptimal adherence, drug-drug interactions and inflammatory reactions (often described in TB as paradoxical reactions). Taken together, these problems have promoted the view that, where possible, antituberculosis therapy should be given initially without HAART.[34] However, retrospective studies suggest that the risk of AIDS events or death is especially high in HIV/TB co-infected patients within the first 2 months of TB treatment if the CD4+ cell count is <100 cells/μL at baseline.[35,36] A balance needs to be established between the risk of further AIDS and death if HAART is deferred against an increased risk of paradoxical reactions and other adverse events if HAART is started rapidly after TB diagnosis. In those for whom concurrent HAART and antituberculosis therapy is deemed appropriate, the evidence upon which to base the decision of precisely when to start HAART remains poorly defined. In practice, we adopt the following approach; those individuals with blood CD4+ cell counts >200 cells/μL can defer HAART until antituberculosis therapy has been completed. If the CD4+ cell count is <200 cells/μL, we prescribe *Pneumocystis* pneumonia prophylaxis; and plan to start HAART within 2 months of commencing antituberculosis therapy. At lower CD4+ cell counts of <100 cells/μL, this delay is often much less; however, it is rare to start concurrent treatment for both conditions, and usually we will initiate HAART a minimum of 1 week after antituberculosis treatment is commenced.

Just as the data addressing the chance of developing AIDS with delayed HAART are limited, so too is that used to calculate the risk of paradoxical reactions, which is largely retrospective or highly selective in its analysis.[37-41] Most studies have suggested an increase in the frequency of paradoxical reactions in individuals commenced on HAART within 2 months of TB diagnosis. Predictors of such reactions at the time of TB diagnosis are not clearly defined, but may include the presence of disseminated TB and low blood CD4+ cell count (e.g. ≤100 cells/μL). However, although life-threatening reactions have been described, in our experience it is possible to manage most of these symptomatically without interruption of either HAART or antituberculosis therapy. Furthermore, we have recently

shown in a retrospective cohort study that the incidence of adverse events not related to paradoxical reactions is unrelated to the time from TB treatment at which HAART is started.[42] Clearly, more prospective data are needed to inform clinical decision making.

The optimal regimen for combined use of HAART and antituberculosis therapy also remains to be defined. A large body of data from both drug trials and observational cohorts in HIV-infected individuals has shown the sustained positive effects on HIV viral load, blood CD4+ cell count and clinical outcome if the initial HAART regimen contains either a PI or a NNRTI.[28,29] Currently, there are little data demonstrating similar responses in specific HIV/TB co-infected populations, but what does exist is encouraging.[43,44] It is important to note that in many settings with a high burden of TB, the choice of HAART regimen is much more likely to reflect local antiretroviral availability than virological potency or potential drug-drug interactions.[45]

As discussed in section 1, the CYP enzyme system plays an important role in the metabolism of PIs, NNRTIs and rifamycins. Combining these agents may produce both enzyme induction and inhibition, so adequate care must be taken to avoid subtherapeutic as well as toxic administration. Rifampicin is a potent inducer of CYP enzymes, producing marked reductions in plasma concentrations of both single and ritonavir-boosted PIs. Consequently, rifampicin should ideally be avoided with PI-based regimens, although specific combinations may be possible with careful monitoring if no other HAART regimen is available.[46] Non-rifamycin-containing TB regimens are markedly less potent, have to be administered for a far longer duration and are not recommended except in situations where the only HAART options are those containing PIs or when rifamycins are otherwise contraindicated. The metabolism of rifabutin is inhibited by PIs and, thus, dose reduction is required.[47] With unboosted regimens, a 50% dose reduction to 150 mg/day is sufficient and with boosted regimens 150mg three times weekly appears optimal, although little data exist to support the latter.[44]

The effect of rifampicin in inducing the metabolism of NNRTIs is not as marked as with PIs. Rifampicin has been demonstrated to reduce the mean peak (C_{max}) and trough (C_{min}) plasma efavirenz concentrations as well as the area under the concentration-time curve (AUC) by >20%, although with a marked degree of interpatient variability.[48] These effects can be overcome by increasing the administered dosage of efavirenz from the standard 600 mg/day to 800 mg/day for individuals >50kg in weight. We have reported good virological outcomes in patients treated with efavirenz 800 mg/day if >50kg.[44] However, another study of mainly Black-African patients treated in the UK with this dosage regimen reported high drug levels and toxicity in seven of nine individuals.[49] A randomised, controlled study in a Thai population with a median weight of 50kg comparing efavirenz 600 mg/day with 800 mg/day administered concurrently with a rifampicin-containing antituberculosis regimen found no difference in median plasma efavirenz concentrations between the two groups, and no differences in virological or immunological responses at 48 weeks.[50,51] The authors cautioned that it may not be possible to extrapolate their findings to other racial populations. However, similar data have been reported from South America (though again with a relatively low mean weight of 51kg).[52] An Indian study[53] has also demonstrated similar immunological responses in individuals receiving efavirenz with and without concomitant rifampicin. We conclude from this data that efavirenz and rifampicin can be successfully combined with good outcomes for both HIV and TB. However, the optimal dosage of efavirenz and the role of therapeutic drug monitoring in establishing this on an individual basis remain to be established. Provided the patient is not overwhelmed by efavirenz-related adverse effects, it would seem sensible to use 600 mg/day in those weighing <50kg and 800 mg/day if heavier than this. It is also possible to combine the use of efavirenz with a rifabutin-containing antituberculosis regimen. This combination causes a reduction in plasma rifabutin levels which can be adequately compensated for by increasing the rifabutin dose to 600mg if using a twice weekly

regimen.[54] Considering the risk of treatment failure with highly intermittent administration in HIV-infected individuals,[20] we believe that when possible treatment should be taken daily. Here, the manufacturers advise that rifabutin should be increased to 450 mg/day, although there are little data to support this.[32]

The NNRTI nevirapine is often used in a fixed-dose generic HAART regimen in resource-poor settings.[55] Because most of these areas have a high burden of TB, the ability to combine nevirapine with antituberculosis therapy is essential. Rifampicin has been demonstrated to reduce the nevirapine AUC, C_{max} and C_{min} by 31%, 36% and 21%, respectively, with no significant effect on rifampicin concentrations.[56] However, the high therapeutic index for nevirapine may mean that these reductions do not translate in to worse clinical outcomes.[57] For example, although there was a significantly lower plasma nevirapine concentration when rifampicin was co-administered with nevirapine 400 mg/day, 86% of individuals had therapeutic nevirapine concentrations.[58] It has also been reported in seven individuals that subtherapeutic nevirapine concentrations seen with rifampicin co-administration may be overcome by an increase in the nevirapine dosage from 400 mg/day to 600 mg/day.[59]

There are currently a paucity of data with which to assess clinical outcomes using nevirapine and rifampicin. Concerning the 32 individuals treated in an observational study[60] with rifampicin 600 mg/day and nevirapine 400 mg/day, 74% achieved undetectable viral loads (<400 copies/mL) after 6 months. A study of 140 HIV-infected Thai patients receiving nevirapine 400 mg/day with or without rifampicin, demonstrated significantly lower plasma nevirapine concentrations at 8 and 12 weeks in those receiving rifampicin, but no differences in blood CD4+ cell count or the proportion achieving a plasma HIV load <50 copies/mL at week 24 between the two groups.[61] Thus, the available data suggest that nevirapine-based HAART can be used in HIV-infected individuals being treated for active TB. However, more clinical outcome studies are needed, especially in resource-poor settings.

Nucleoside reverse transcriptase inhibitors (NRTIs) can be easily combined with rifamycin-containing antituberculosis regimens. The suggestion that a triple NRTI regimen could have equivalent potency to other HAART regimens has led some experts to advocate this as the optimal combination for individuals requiring concomitant anti-HIV and antituberculosis therapy.[34] However, an increasing amount of data have demonstrated that such a regimen is less effective than others available for both HAART-naive and -experienced individuals.[62,63] The recent report of the successful use of the antiretroviral combination of zidovudine with lamivudine and tenofovir (a nucleotide reverse transcriptase inhibitor) in sub-Saharan Africa may lead to further studies within TB treatment regimens.[64]

It is likely that novel antiretroviral agents will become available in the near future and these will require careful evaluation with respect to interactions with antituberculosis drugs. The HIV fusion inhibitor, enfuvirtide, is one such agent that is available for the treatment of antiretroviral-experienced individuals. There appears to be no interaction between enfuvirtide and rifampicin, and so its use concurrently with antituberculosis regimens should not be problematic.[65] Table I contains a summary of potential interactions and necessary dosage adjustments required when combining antiretroviral agents with antituberculosis regimens containing rifamycin.

The majority of individuals with HIV and TB co-infection will be diagnosed with TB prior to starting HAART. It is worth noting though that in both resource-poor and resource-rich settings, a significant proportion of TB (up to 20%) will be diagnosed in individuals already receiving HAART.[66,67] Whilst it has been shown that antiretrovirals will reduce the overall risk of active TB by between 70% and 90%,[68] it can still occur at any time after starting HAART. This is the case even when the apparent response to HAART has been satisfactory. There are an increasing number of reports which suggest that TB diagnoses are especially common soon after HAART is commenced.[69,70] The reasons for this are unclear. Possible explanations include

Table I. Potential interactions and dose adjustments required when combining antiretroviral drugs with rifamycin antituberculosis therapy

Antiretroviral	Advice
NRTI	
Zidovudine	No significant interaction. No dose adjustments required
Stavudine	No significant interaction. No dose adjustments required
Didanosine	No significant interaction. No dose adjustments required
Lamivudine	No significant interaction. No dose adjustments required
Zalcitabine	No significant interaction. No dose adjustments required
Abacavir	No significant interaction. No dose adjustments required
Emtricitabine	No significant interaction. No dose adjustments required
Tenofovir[a]	No significant interaction. No dose adjustments required
NNRTI	
Nevirapine	Potential interaction. Avoid if possible. May need a dose increase of nevirapine (see section 2)
Efavirenz	Potential interaction. May need efavirenz dose increase to 800mg with rifampicin if >50kg (see section 2). Increase rifabutin dose (see section 2)
Delavirdine	Significant interaction. Avoid with rifampicin and rifabutin
PI	
Single PI ritonavir	Significant interaction, avoid with rifampicin. Can combine with rifabutin
Unboosted indinavir	Significant interaction, avoid with rifampicin. Decrease dosage to rifabutin 150 mg/day
Unboosted saquinavir	Significant interaction, avoid with rifampicin. Decrease dosage to rifabutin 150 mg/day
Unboosted nelfinavir	Significant interaction, avoid with rifampicin. Decrease dosage to rifabutin 150 mg/day
Unboosted amprenavir	Significant interaction, avoid with rifampicin. Decrease dosage to rifabutin 150 mg/day
Unboosted lopinavir	Significant interaction, avoid with rifampicin. Decrease dosage to rifabutin 150 mg/day
Unboosted fosamprenavir	Significant interaction, avoid with rifampicin. Decrease dosage to rifabutin 150 mg/day
Unboosted atazanavir	Significant interaction, avoid with rifampicin. Decrease dosage to rifabutin 150 mg/day
Unboosted tipranavir	Significant interaction, avoid with rifampicin. Decrease dosage to rifabutin 150 mg/day
Ritonavir-boosted PI	Significant interaction, avoid with rifampicin. Decrease dosage to rifabutin 150mg three times weekly
Fusion inhibitor	
Enfuvirtide	No significant interaction. No dose adjustments required

a Tenofovir is a nucleotide reverse transcriptase inhibitor.

NRTI = nucleoside reverse transcriptase inhibitor; **NNRTI** = non-nucleoside reverse transcriptase inhibitor; **PI** = protease inhibitor.

that these individuals already had active TB that has now been recognised through more careful medical surveillance, or that HAART itself has in fact 'unmasked' a subclinical infection that is driven by the newly restored immune response.[69] The practical therapeutic consequence is that at the time of commencing antituberculosis therapy it may be necessary to alter the HAART regimen in view of the potential drug-drug interactions already noted. However, it is usually possible to continue HAART without interruption. A further issue that merits study is how latent or subclinical TB can be most effectively identified prior to commencing HAART.

3. Management of Adverse Events in HIV/TB Co-Infection, Including Paradoxical Reactions

One of the potential obstacles to the successful treatment of HIV and TB, whether or not this is concurrent, is the occurrence of adverse events. It has been reported that these are more frequent in HIV/TB co-infected patients.[71] Prior to use of HAART this may have reflected the additional toxicity of therapy for other opportunistic infections or that due to specific antituberculosis agents such as thioacetazone.[14,72] In line with previous work, we have noted serious adverse events (grade III or IV)

to be more common in a population of HIV/TB co-infected individuals receiving daily rifamycin-based antituberculosis regimens (71% of whom received concomitant HAART) than in individuals not infected with HIV treated with similar antituberculosis treatments.[42,73] Persistent vomiting and peripheral neuropathy, in particular, were significantly more frequent in the HIV infected group.

The most common reason for antituberculosis treatment interruption in our study was hepatotoxicity (13% in both groups) and this generally occurred in the first 2 months of treatment. Somewhat surprisingly, this did not occur any more frequently in the HIV infected group, despite a number of antiretroviral agents having been noted to cause liver function test abnormalities.[74] The frequency of TB therapy interruption, premature discontinuation of therapy and relapse did not differ between the two groups.[42]

If hepatotoxicity does occur, re-introduction of antituberculosis therapy can be achieved by the sequential addition of isoniazid, rifamycin and pyrazinamide. Each agent should be increased to its standard dosage over 2–3 days, with a period of observation between restarting each agent of a further 2 or 3 days.[9] It should be noted that pretreatment liver function tests are often mildly abnormal and that a transient worsening of blood tests may be initially observed when therapy is commenced. If at all possible, clinicians should try to avoid prescribing drug combinations with overlapping toxicities. For example, isoniazid and stavudine used together appear to increase the risk of peripheral neuropathy.[35,75] However, we recognise that this may not be practicable and adverse events then need to be managed symptomatically, with the aim of maximising adherence to therapy.

The management of paradoxical reactions (often but not exclusively seen as part of the immune reconstitution inflammatory syndrome) remains poorly defined and is largely based upon anecdote and expert opinion. We have already discussed the uncertainty that exists regarding predisposition to paradoxical reactions. A better understanding of this would enable increased avoidance of this phenomenon. In particular, no evidence exists to demonstrate that paradoxical reactions are any more common using a particular HAART-regimen. Its manifestations are very variable and, thus, management requires a number of complementary strategies. An important first step must always be to exclude as far as possible drug toxicity, progressive disease as a result of poor adherence, resistance to therapy, malabsorption, inadequate drug concentrations due to drug-drug interactions or the presence of an alternative diagnosis such as lymphoma or another infection.

Generally, paradoxical reactions can be managed without the interruption of either antituberculosis therapy or HAART, although the latter might be indicated with life-threatening reactions. Transient radiological worsening that resolves spontaneously is not uncommon and here the most important therapeutic role of the physician is to provide reassurance.[76] In more symptomatic or prolonged cases, treatment needs to be tailored to the specific scenario.

Life-threatening worsening of cerebral or mediastinal disease that is likely to cause compression of vital structures should be treated with systemic corticosteroids. The required dosage is unclear. Prednisolone (or equivalent) of between 20 mg/day and 80 mg/day is suggested as being adequate.[39,77] Treatment duration also needs to be better defined. Empirically, most clinicians tend to treat for 2–4 weeks, with a dose taper about half way through the course.

Palpable lymph node swelling tends to respond well to corticosteroid therapy, although the avoidance of corticosteroid-related adverse events may be achieved by the expeditious use of needle aspiration. This can be repeated regularly if necessary, as advocated for paradoxical reactions in patients who are HIV negative.[78] Some experts have suggested a role for NSAIDs, although the evidence base for this is small.[77] More specific immunomodulatory agents may in time be demonstrated to be more effective, although the use of such targeted therapy will require a better understanding of the relevant mechanisms involved.

4. Conclusions

The prognosis of many individuals with HIV/TB co-infection has greatly improved following the introduction of HAART. If it is available and careful attention is paid to the possible drug-drug interactions, then it is perfectly possible to combine effective antituberculosis and anti-HIV therapy with good overall outcomes. Future work needs to establish the optimal regimens that can be delivered in resource-poor settings, as well as the optimal time at which to start HAART.

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Correspondence and offprints: Dr *Ronan A.M. Breen*, Department of Thoracic and HIV Medicine, Royal Free Hospital, Pond Street, London, NW3 2QG, UK.
E-mail: r.breen@medsch.ucl.ac.uk