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Review editorial: **Prevention of tuberculosis in resource-poor countries with increasing access to highly active antiretroviral treatment**

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Summary The administration of isoniazid (INH) has been proposed, evaluated and implemented to prevent tuberculosis (TB) disease among patients who are infected with the human immunodeficiency virus (HIV). This strategy has been developed in communities where TB is highly endemic and at a time when antiretroviral (ARV) treatment was not, or was rarely available. Although INH prevention programmes were somewhat pushed to the background due to the worldwide advocacy for ARV drugs, prevention of TB remains of paramount importance. The dual HIV–TB infection poses problems, not only for the individual and his/her clinician but also for the programme manager. We review various aspects of TB preventive treatment in countries with a high prevalence of HIV–TB co-infection and limited resources but with increasing access to ARV treatment.

keywords tuberculosis, prevention, highly active antiretroviral treatment, human immunodeficiency virus infection, countries with limited resources

Introduction

Treatment of latent tuberculosis (TB) infection, also referred to as preventive therapy or chemoprophylaxis, has been proposed as a useful intervention to improve the quality-of-life of human immunodeficiency virus (HIV) infected individuals (Wilkinson *et al.* 1998). The epidemiological rationale behind this intervention can be summarized in one sentence: people who are infected with HIV and who have a positive tuberculin skin test have a 30% or higher lifetime risk of developing active TB (Selwyn *et al.* 1989; Guelar *et al.* 1993) and TB is the most common HIV related disease in developing countries (Halsey *et al.* 1998). To introduce this preventive therapy on a wide scale, isoniazid (INH) preventive programmes have been designed and implemented, ideally based on the guidelines as stipulated by the World Health Organization (WHO) and the International Union Against TB and Lung Diseases (IUATLD) (WHO Global Tuberculosis Programme & UNAIDS 1998). If followed rigorously, a well-designed programme requires human resources and infrastructure that may be major constraints for a successful implementation. To name just a few of the stumbling blocks: one must exclude active pulmonary tuberculosis (PTB) before starting the chemoprophylaxis and after having started one must guarantee patient compliance to the drugs during the stipulated period. Lack of integration between TB and HIV programmes has caused long delays in the implementation of these useful interventions.

As a result these programmes have not taken root as fast as one would expect in countries with a high burden of HIV and TB (Godfrey-Faussett & Ayles 2003). Now that we have entered the era of rolling out of antiretroviral treatment (ART) programmes (Kapp 2004), a new way of thinking about the interaction between TB and HIV arises: does TB chemoprophylaxis still deserve the attention it had, with antiretroviral (ARV) drugs becoming more and more accessible? Should we not focus our attention and limited resources to the implementation of ART programmes, and consider INH prophylaxis as a lost opportunity in the past? This review compiles the evidence regarding TB treatment and TB preventive treatment in the presence of HIV infection and suggests ways to integrate preventive treatment in low resource settings where ARV drugs are available, thereby identifying the remaining gaps in our current knowledge.

Tuberculosis treatment in the presence of human immunodeficiency virus infection

It is widely accepted that HIV infected individuals who develop TB greatly benefit from anti-TB therapy: the cure rates are similar to HIV negative patients (Connolly *et al.*

1999). The overall mortality, however, is significantly higher, increases with the severity of immune deficiency, and is due to complications of HIV, not TB (Chaisson *et al.* 1987; Ackah *et al.* 1995). This and the incidence of AIDS defining illnesses can be reduced by the co-administration of ART (Mocroft *et al.* 1998) and anti-TB drugs, but at a price, as will be discussed later.

Patients who have symptomatic HIV disease before the start of TB treatment have a high risk of recurrent TB, as demonstrated by Fitzgerald in Haiti: HIV-positive individuals had a 10-fold greater risk of recurrent TB than HIV-negative individuals after completion of a 6-month rifampicin (RIF)-containing regimen. Half of the recurrences occurred after 18 months of post-treatment follow up, and all cases of recurrent TB were in patients who had symptomatic HIV disease before the onset of TB (recurrence rate of 13.4 per 100 person-years)(Fitzgerald *et al.* 2001). A high recurrence rate of TB in HIV+ individuals may have a number of consequences. Cure rates in recurrent TB are lower, five-drug re-treatment regimens are longer and more expensive with more drug related adverse effects and it is also more difficult to achieve compliance.

Tuberculosis preventive treatment in the presence of human immunodeficiency virus infection: microbiological and efficacy data

Preventive therapy (treatment of infected persons to prevent the progression of latent infection to clinical disease) is based on the widely accepted theory that primary infection with *Mycobacterium tuberculosis* (MTB) is followed by a latent phase in the majority of patients, with tubercle bacilli surviving for a long time in a dormant condition (Davies 1998b). TB disease results from reactivation of these dormant bacilli when triggered by certain conditions (Lucas 1988).

Chemoprophylaxis (treatment to prevent infection and subsequent disease) should be used for populations where high TB incidences are observed in the HIV infected subpopulation of which a large proportion is the result of recent infection (Sonnenberg *et al.* 2001; Lambert *et al.* 2003).

While the mechanism of preventive therapy is not known, it is assumed that administration of INH results in sterilization of infection and elimination of organisms from infected persons (Houk *et al.* 1968). Follow-up studies have shown that the duration of protection in areas where the rate of new infection is low is at least 19 years (Comstock *et al.* 1979). The picture is totally different in areas with high (re)-infection rates where INH alone as preventive treatment has an efficacy of only 18 months, whereas 3 months regimens with RIF and pyrazinamide or RIF and INH are efficacious during 3 years (Johnson *et al.* 2001). Studies that support re-infection as the major cause of relapse in HIV infected people living in high TB prevalence areas provide further support to the suggestion that the efficacy of preventive therapy may not be long term (Casado *et al.* 2002). In this case it would be logical to suppose that prophylaxis is necessary as long as the risk factor is present.

Studies that were key markers in providing evidence of the possible benefit of TB preventive therapy on TB disease incidence in HIV infected individuals were carried out in Haiti, Mexico, Zambia, Kenya, Uganda and Thailand. Several meta-analysis were subsequently held and updated (Wilkinson *et al.* 1998; Bucher *et al.* 1999). The most recent and extensive analysis was carried out by Woldehanna and Volmink (2004) and was based on 8130 randomized participants. They came to the following conclusions: preventive therapy (any anti-TB drug) *vs.* placebo is associated with a lower incidence of active TB [RR: 0.64 (0.51–0.83)]. This benefit is more pronounced in individuals with a positive tuberculin skin test [RR: 0.38 (0.25–0.57)] than in those who have a negative test [RR: 0.83 (0.58–1.18)]. Overall there is no evidence that preventive therapy *vs.* placebo reduces all-cause mortality [RR: 0.95 (0.85–1.06)] although a favourable trend is found in people with a positive tuberculin test [RR: 0.80 (0.63–1.02)].

Which regimen to use for tuberculosis preventive treatment?

Several drug regimens have been subject to controlled trials: using INH alone, INH in combination with RIF or RIF and pyrazinamide containing regimens, or RIF and pyrazinamide (Halsey *et al.* 1998). Meta-analysis data indicate that efficacy was similar for all regimens, at least in the short term. However, compared to INH monotherapy, short-course multi-drug regimens were much more likely to require discontinuation of treatment due to adverse effects (Gordin *et al.* 2004; Saukkonen 2004). INH is therefore recommended by the WHO/UNAIDS as a daily, self-administered therapy for 6 months (WHO Global Tuberculosis Programme & UNAIDS 1998).

The same drug is used for secondary prophylaxis: in Haiti post-treatment INH prophylaxis for 1 year reduced the incidence of recurrent TB by 80%, but post-treatment INH prophylaxis did not prolong survival (Fitzgerald *et al.* 2001).

In a cohort of South African gold miners, secondary prevention using INH 300 mg/day for an indefinite period reduced the incidence of TB by 55%. This difference was especially tangible in the group of patients with advanced disease and low $CD4^+$ lymphocyte counts (Churchyard *et al.* 2003).

Tuberculosis preventive therapy in the presence of human immunodeficiency virus infection: programme aspects

Treatment of latent TB infection has long been considered as a public health intervention that could prevent latent TB from progressing to TB disease in the infected individual and at the same time an intervention that could have an impact on TB transmission by reducing the progression to infectious cases. However, there has never been an internationally accepted consensus among experts to introduce preventive programmes on a wide scale (Davies 1998a). Some industrialized countries have introduced this intervention on a public health scale (American Thoracic Society 1983), others have limited its application to strictly defined individual cases.

Well aware of the possible risks of further compromising the already overstretched TB programmes, WHO and UNAIDS set out a series of conditions that needed to be fulfilled before TB PT could be recommended (WHO Global Tuberculosis Programme & UNAIDS 1998). These conditions defined requirements to identify HIV-positive subjects, to screen them to exclude active TB, to target those most likely to be infected with MTB (either by PPD skin test or by identifying high risk groups), to provide them with drugs and to monitor and follow them up to guarantee compliance. These conditions were further inspired by the ever looming risk of inducing resistance against one of the most cost-effective bactericidal anti TB drugs at the TB programme manager's disposal.

The pro-test initiative was one example how to operationalize combined TB/HIV reduction activities (Godfrey-Faussett *et al.* 2002). The promotion of voluntary counselling and testing (VCT) was seen as an entry point for access to the core interventions of intensified TB case-finding and INH preventive treatment. The benefits of VCT for HIV–TB patients include referral for appropriate clinical care and support for those testing HIV-positive. Likewise, people attending a centre for VCT can benefit from TB screening: those found to be both HIV-positive and with active TB need referral for TB treatment and cotrimoxazole prophylaxis; those without active TB should be offered TB preventive treatment with INH.

It can hardly be said that INH preventive programmes became a success story everywhere: the few feasibility studies done in operational circumstances that were published showed limited results in terms of numbers treated and adherence (Aisu *et al.* 1995). Constraints mentioned were, among others: limited motivation and knowledge by counsellors to discuss TB issues during HIV pre- and post-test counselling, insufficient availability of medical screening, insufficient sites to collect pills, and frequent tuberculin-negative tests.

Tuberculosis prevention programmes and tuberculosis transmission

The international community has adopted early, passive case finding and treatment of infectious, sputum positive cases as the prime strategy to reduce the infection rate of pulmonary TB (Rodrigues & Smith 1990; WHO 1994). PTB incidence rates have dropped dramatically in industrialized countries and the same was observed in a substantial number of developing countries, at least, before the rise of the HIV epidemic. Whether this drop was due to the chosen strategy or due to improved socio-economic conditions, cannot be established and has only academic importance. It remains a fact though that transmission occurs before cases are detected, and is reduced to neglectable levels soon after the patient is put on treatment. In theory, preventive therapy should have a more direct impact on transmission, as cases are treated before they ever become infectious. Moreover detection rates could be pushed up by actively screening for TB as part of the procedure for eligibility for INH preventive therapy.

For preventive therapy to have any impact, however, the scale of preventive therapy services should be expanded greatly (Godfrey-Faussett *et al.* 2002). Some authors tried to answer the question to what level they should be expanded, by entering different scenarios in computer models. Corbett *et al.* (2002) came to the conclusion that combined approaches that tackle both latent TB and ongoing TB transmission are likely to be most successful, particularly when not exclusively targeted to those of known HIV status. Caution needs to be exerted, however, as some assumptions and estimations in these models are based on observational TB studies carried out before the HIV era.

Tuberculosis prevention in times of highly active antiretroviral treatment (HAART)

It has been demonstrated in South Africa that a substantial impact on TB disease incidence can be expected from ART: HAART reduced the incidence of HIV-1 associated TB by more than 80% in an area endemic with TB and HIV-1 (Badri *et al.* 2002). The greatest number of TB cases averted by HAART was in the subset of patients with baseline WHO stage 3 or 4 or CD4 counts below 200. In patients with a CD4 count of more than 350 cells/μl there was no difference in TB incidence. The authors concluded that TB preventive therapy might be a more attractive alternative for reducing the risk of TB in patients with CD4

counts between 200 and 350 cells/μl. In this group of patients it is likely to be more feasible to exclude active TB than in patients who have advanced HIV disease.

So far, all TB prophylaxis trials have been performed in persons who were not receiving ART. These trials have often been performed in VCT sites including persons who were asymptomatic or pauci-symptomatic and without severe immune deficiency. Today we need to determine when and which TB prophylaxis regimens could be used in symptomatic patients and/or patients with severe immune deficiency who meet the criteria for starting ART.

Tuberculosis prophylaxis regimens in times of highly active antiretroviral treatment: opportunities

Taking INH everyday can give an idea of the adherence potential of the patient, invaluable information in view of its importance once the patient eventually needs ART. Reducing the incidence of TB among persons with HIV treated with HAART is essential because TB complicates the management of HAART treated patients, leading to a reduced efficacy of the HAART regimen with the development of resistance and potential spread of resistant viruses as a consequence.

Tuberculosis prophylaxis regimens could reduce the risk of the immune reactivation inflammatory syndrome (IRIS) once ART is started. This syndrome is caused by a reviving immune response to opportunistic organisms such as MTB. Narita has reported the incidence of IRIS to be as high as 36% when ART is started a mean of 8 weeks after initiation of TB therapy (Narita *et al.* 1998). Others have reported an increased IRIS incidence when ART is started earlier, in subjects with low CD4 counts, and in those with both pulmonary and extra-pulmonary disease (Wendel *et al.* 2001; Navas *et al.* 2002). This temporal relationship suggests that paradoxical reactions in HIV-infected patients are due to restoration of immunity toward mycobacterial antigens (Foudraine *et al.* 1999). The management of TB–IRIS has not been well studied, but this condition potentially could lead to the discontinuation of ART.

With the increased access to ART in countries with high HIV and TB prevalence, centres providing these drugs are presently overwhelmed by patients with HIV–TB co-infection. TB chemoprophylaxis potentially could reduce the nosocomial transmission of TB in HIV treatment centres. Nosocomial transmission of TB among clinic/hospital patients as well as TB–IRIS could undermine the confidence of patients in the medical services provided and therefore may have a negative effect on treatment adherence. Moreover TB re-infections during HAART complicate the management of the patient: physicians may wrongly consider such a TB episode to be a consequence of an inadequate previous TB treatment or a consequence of an ineffective ART and therefore take the wrong therapeutic decisions.

For any group of patients that has been on ART, and where the treatment is interrupted because of therapeutic failure, supply problems, financial barriers or any other reason, INH chemoprophylaxis together with cotrimoxazole can be considered. In how far this will prevent the risk of TB (re-)infection should be investigated.

Tuberculosis prophylaxis regimens in times of highly active antiretroviral treatment: challenges

HAART is started in countries with limited resources in patients in WHO stage 3 or 4 or with CD4 counts below 200 cells/μl. Before considering TB prophylaxis in these patients the presence of active TB should be excluded. There is a high probability that these symptomatic patients do have either latent or even clinical TB, which cannot be diagnosed because of the lack of sensitive diagnostic tests in resource-poor settings (Colebunders & Bastian 2000).

Research questions to be addressed

- What is the most cost beneficial way to exclude active TB in patients starting HAART?
- Can the incidence of TB–IRIS be reduced by the administration of anti-TB drugs – which drugs and how long – prior to the initiation of HAART?
- Should TB prophylaxis be continued in patients on HAART – and how long? Should prophylaxis be stopped based on CD4 count results?
- Should TB prophylaxis be continued – and how long – after full TB treatment in patients on ART? Should TB prophylaxis be stopped based on CD4 count results?
- Should TB prophylaxis be considered in cases of ART interruption and if yes what need to be the criteria to start such prophylaxis?
- What is the feasibility of integrating a TB prophylaxis in an ARV roll out programme in settings with limited laboratory and X-ray facilities, insufficient funding and lack of human resources?

Operational research and prospective randomized controlled trials are urgently needed to answer these questions.

Conclusion

Research in countries with limited resources has shown that TB prophylaxis may be beneficial for patients with

HIV infection. However, very little is known about how to implement large-scale TB prophylaxis in countries with limited resources with increasing access to ART. In the era of the three by five initiative, TB prophylactic strategies that were proposed in the past should be re-evaluated and new strategies need to be tested.

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