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Antiretroviral therapy and tuberculosis: does the regimen matter?

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Infection with HIV is one of the strongest drivers of the incidence of tuberculosis. The use of potent combination antiretroviral therapy (cART) decreases the incidence of tuberculosis in HIV-infected patients. Data on whether this effect differs by type of initial antiretroviral drug or regimen are scarce. Studies are often not designed to address the potential effect of cART on tuberculosis incidence, and/or the diagnosis of tuberculosis is poorly validated. The paucity of data precludes recommendation on the initial cART regimen with respect to the incidence tuberculosis. Other well-described intervention like preventive therapy, and early start with cART are likely to have more effect on the prevention on tuberculosis in HIV-infected patients.

Infection with HIV is one of the strongest drivers of the incidence of tuberculosis. The current use of potent combination antiretroviral therapy (cART) inhibits HIV replication, resulting in immune preservation and reconstitution, and a marked decrease in the incidence of tuberculosis. A recent meta-analysis including both clinical trials and observational studies showed a consistent reduction in tuberculosis incidence among HIV-infected patients starting cART across a multitude of levels of immunosuppression [1]. The pooled effect size was a 65% reduction and similar to that seen in an earlier meta-analysis that also included studies from developed countries [2].

Current guidelines for cART are highly standardized with respect to initial regimens, especially in developing countries where a particular initial regimen is often dependent on governmental guidance, local availability or even international funding. The risk of tuberculosis during cART is not part of the decision process of which regimen to initiate, as it is assumed that it is primarily driven by immunological parameters. While cART reduces the risk of tuberculosis, this risk remains higher than in the HIV-uninfected population, which can be considerable in countries with a high burden of tuberculosis. Any differential effect of different cART regimens on the risk of tuberculosis could therefore impact tuberculosis-related morbidity and mortality in the HIV-infected population.

Information on this potential differential risk for tuberculosis is sparse. Observational studies comparing regimens consisting of two nucleoside-analog reverse transcriptase inhibitors plus either a protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI) gave inconclusive results despite large sample sizes. The usefulness of observational studies to answer this research question is questionable. Non-randomized treatment allocation is driven by the clinical situation of the patient and availability of drugs, a phenomenon referred to as 'bias by indication'. This bias confounds the reported associations between treatment regimen and outcome measures. It is possible to mitigate this bias by applying adequate statistical methodology which results in an appropriate control of confounding by, in effect, mimicking the randomization process. Propensity scores and marginal structural models are increasingly finding their way into epidemiological research.

Keywords: antiretroviral therapy • HIV • IPT • study design • tuberculosis

EXPERT REVIEWS

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Using the propensity score methodology, we recently reported on an unexpected increased risk for tuberculosis in patients starting their initial cART with a regimen containing efavirenz compared with those starting with nevirapine [3]. Up to then there had been no reports of a differential risk between these two NNRTIs. The study included almost 6000 HIV-infected patients starting cART in a large urban HIV clinic in Kampala, Uganda. The risk of tuberculosis was twice as high for patients starting their cART with an efavirenz-containing regimen at a $CD4^+$ T-cell count of less than 100 cells/mm^3, compared with patients starting a nevirapine-containing regimen at the same level of immunosuppression.

Randomized controlled trials are much better placed to assess the association between different cART regimens and the incidence of tuberculosis. Unfortunately, this outcome is hardly ever reported, and when it is, it is done in the context of an adverse events analysis in which it is not always clear how well the diagnosis is assessed and validated. The two largest randomized clinical trials comparing the efficacy of the NNRTIs nevirapine and efavirenz did not report on the incidence of tuberculosis [4,5].

The more recently concluded OCTANE trial comparing the efficacy of the PI lopinavir and the NNRTI nevirapine in women did not formally report on difference in tuberculosis incidence. However, re-analyzing the limited data presented in the text and tables identified a significantly lower incidence of tuberculosis in participants randomized to lopinavir compared with those randomized to nevirapine [6]. Although not a formally defined outcome, 4% of women in the former group were reported to develop or die from tuberculosis compared with 10% in the latter group, despite a similar efficacy of the cART regimens. A large randomized trial comparing initial treatment with lopinavir and efavirenz did not report on the incidence of tuberculosis but stated that there were no differences in the incidence of AIDS-defining events (which include tuberculosis) [7]. Randomized trials comparing NNRTIs and the PI atazanavir did not report on the incidence of tuberculosis [8,9], nor did randomized trials comparing lopinavir, with the PIs atazanavir or darunavir [10,11].

From the paucity of available data follows that tuberculosis incidence in relation to initial cART regimen has seldom been a primary research question. As such, the reported data should be considered cautiously because most study designs are not appropriate for addressing this issue. Even if they are, it remains often unclear how the main outcome (tuberculosis) was assessed and the diagnosis validated. The study by Hermans *et al.* tried to address important methodological issues, but the *post-hoc* analysis remains open to residual confounding and bias [3].

The observations on lopinavir and efavirenz should merely serve as generating hypotheses. As such, they are unexpected and intriguing. They might be related to phenomena that are not yet well understood. It has been suggested that the PIs influence proteasome activity *in vitro* in addition to their known effect on viral enzymes [12,13]. The proteasome has recently been identified as a potential drug target in the treatment of *Mycobacterium tuberculosis* [14], possibly explaining why the incidence of tuberculosis during PI-containing ART might be reduced. The use of efavirenz is associated with reduced vitamin D concentrations in plasma, while vitamin D deficiency is associated with an increased risk of tuberculosis [15,16].

To date, the evidence of differential effects of antiretroviral drugs on the incidence of tuberculosis seems to be too speculative to form a basis for firm guidance on the choice of the initial cART regimen. In the quest to reduce tuberculosis morbidity and mortality in the HIV-infected population, wider implementation of tuberculosis-control strategies with proven effectiveness are likely to have a larger impact.

Isoniazid preventive therapy (IPT) reduces the incidence of tuberculosis in HIV-infected individuals [17]. One of the drawbacks is the need to exclude active tuberculosis before starting IPT to prevent accidental monotherapy for tuberculosis. Both the screening of HIV-infected individuals for active tuberculosis and the provision of IPT for those without tuberculosis lag behind international targets for coverage [18]. A sensitive test to diagnose tuberculosis in immunocompromised individuals would be a major stimulus to improve implementation of this intervention. The most effective strategy to prevent tuberculosis in HIV-infected individuals is likely to provide early access to cART to reverse, or at least prevent further deterioration of, the immunodeficiency. Both in high- and low-income countries, large groups of patients start their initial cART regimen at $CD4^+$ T-cell counts below 200 cells/mm^3, despite major expansion in the global roll-out of cART [19,20].

Tuberculosis is a major threat for HIV-infected individuals in countries with high burden of tuberculosis. Improved implementation of known effective strategies will have a marked impact on morbidity and mortality in this population. The possible differential effects of individual antiretroviral drugs on the incidence of tuberculosis need to be explored in studies with adequate designs and analytical approaches to address this question.

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