Dear Editor,

Tuberculosis (TB) is still a major global health problem in 2017, being one of the top ten causes of death worldwide, even though a timely diagnosis and a correct treatment can allow full recovery from the disease. According to the 2016 World Health Organisation (WHO) Global Tuberculosis Report, there were 10.4 million new TB cases and 1.8 million related deaths in 2015, with 1.2 million and 400,000 respectively among HIV-positive people [1].

In late 2015 the WHO endorsed the goals set by both the Sustainable Development Goals and the End TB Strategy whose common targets are 90% reduction in TB deaths and 80% reduction in TB incidence by 2030 compared with 2015 [1-3].

In this context, the prevention of new infections caused by Mycobacterium tuberculosis and of their progression to active disease would have a major role in reducing the burden of TB and related deaths worldwide.

Latent TB infection (LTBI) is the result of the strategy set up by the host in response to M. tuberculosis exposure, and, as it is finalised in limiting the spread of bacilli, it has undoubtedly a protective role [4]. As its efficacy depends on the effectiveness of the immune system, the weaker the latter, the easier the spread of bacilli and the progression from LTBI to active TB disease.

For this reason, the treatment of LTBI is one of the milestones of the health interventions for TB prevention and is particularly important in children under 5 years, whose immune system is not fully developed, and in people with cell-mediated immunodeficiencies (prolonged steroid therapy, chemotherapy, HIV infection, hematologic malignancies, immunosuppressive treatment for solid organ or bone marrow transplantation and autoimmune diseases) [1].

The impact of HIV infection on LTBI is still unclear, as the majority of studies have been performed in high-burden settings, and limited data are available to assess the role of LTBI in low-incidence countries.

Indeed a 2010 meta-analysis of cohort studies evaluating the effect of TB in HIV-infected people and showing that TB was associated with an overall two-fold increase in mortality, did not include any study done in a high-income country [5]. Moreover, when the analysis was restricted to the six studies performed during the antiretroviral therapy era, TB coinfection did not have a significant impact on survival. In settings with low TB transmission, the rate of active TB in HIV-infected individuals with untreated LTBI decreases over time, and most active TB cases occur within the first 2 years of follow-up [6].

The 2010 Cochrane systematic review on the treatment of LTBI in HIV-infected people concluded that therapy reduces the risk of active TB by 32% [7]. However, this result should be balanced against the risk of adverse effects and drug-to-drug interactions, and the evidence
highly active antiretroviral therapy (HAART) itself reduces the progression to active TB by two-thirds [8]. The risk of TB reactivation is likely to decrease further considering that the indications for HAART have been recently widened.

We report our long-term clinical experience on TB in HIV-infected patients.

In a 10-year follow-up study published in 2012, we examined 289 HIV-infected individuals followed at the outpatient HIV Clinic of the Infectious Diseases Unit at Verona University Hospital. Only three patients developed active TB during this 10-year period; none of them was on HAART and two came from TB high-prevalence countries [9]. From January 2014 to July 2017, we have screened with the QuantiFERON TB Gold In-Tube assay (QFT) (Cellestis Limited, Chadstone, Victoria, Australia) all our naïve HIV-positive patients and those already on HAART but never tested for Mycobacterium tuberculosis exposure. Demographic characteristics, clinical records and viro-immunological data were collected. Active TB was ruled out through clinical and, if needed, radiological evaluation. LTBI treatment was actively offered to all the QFT-positive patients with no signs or history of TB.

Overall, we screened 717 patients: 667 (93%) were QFT-negative, 38 (5.3%) positive and 12 (1.7%) had an indeterminate result. The mean CD4+ T lymphocyte count was above 500/mm³ in all the three groups with no significant difference. Only 18 patients had a history of active TB: one had developed the active disease over 10 years before the diagnosis of HIV infection, 14 had a concurrent diagnosis of TB and HIV and 3 developed active TB after the diagnosis of HIV infection, but within the first six months on HAART. Of the subjects with active TB, 8 out of 18 (44.5%) belonged to the QTF-positive group, 10 (55.5%) to the negative group and none to the indeterminate one.

In our cohort, only 3 of 30 patients accepted LTBI treatment and 2 of them stopped it due to isoniazid hepatotoxicity. None of these patients has developed signs or symptoms related to active TB disease so far.

Based on our long-term clinical experience and on the efficacy of HAART in preventing the development of active TB, LTBI treatment in HIV-positive patients on HAART is not needed in high-income countries. Regarding the QTF performance in identifying active TB among HIV-positive patients, our findings show a poor specificity as only 44.5% of subjects with a history of active TB had a QTF-positive result. In the study by Guglielmetti et al., QTF seroconversion showed a limited role in predicting the efficacy of TB treatment in a cohort of HIV-negative patients with active TB [10]. For this reason, we reckon that our QTF low specificity may be more likely related to the unpredictability of QTF seroconversion at the end of the TB treatment, rather than to the HIV-related immunodeficiency, as suggested in another study [11]. Indeed, none of our TB treated-HIV positive subjects had an indeterminate QTF result. The rate of LTBI treatment acceptance varies considerably in the literature; while two studies among Tanzanian HIV-positive patients found an almost perfect acceptance and completion rate, data reported by the North Carolina Division of Public Health showed how challenging is to reach the target percentage of adherence to LTBI treatment in a TB low incidence country [12-14]. Indeed in 2011 Mindachew et al. hypothesized a reverse association between monthly income and LTBI treatment adherence [15]. Several factors may influence the compliance to LTBI treatment among HIV-positive patients living in high-income countries: the burden of pills, the asymptomatic condition of LTBI and, above all, the widespread belief that TB is an old disease which has no importance nowadays. Based on the above considerations and on our experience, it is reasonable to assume that HAART alone can effectively prevent the development of active TB in HIV-infected patients.

Conflicts of interest and source of funding
None to declare.

REFERENCES
The treatment of latent TB infection in HIV-positive people: the Verona experience


