Reviewer's report

**Title:** Improved Sensitivity of an Interferon-Gamma Release Assay (T-SPOT.TB) in Combination with Tuberculin Skin Test for the Diagnosis of Latent Tuberculosis in the Presence of HIV Infection

**Version:** 2  **Date:** 12 September 2011

**Reviewer:** Christoph Stephan

**Reviewer's report:**

Reactivation of tuberculosis (TB) remains a major concern for HIV infected individuals and diagnosis of latent TB-infection is the precondition to control its’ reactivation. Interferon-Gamma-releasing assay (IGRA), i.e. QuantiFERON Gold and T-Spot.TB (Elispot assay), is a major diagnostic step forward, thus it has become standard of care recently; however both tests’ sensitivity still could be improved.

This paper tested the innovative approach to combine cheap and widespread available tuberculin skin test (TST) and modern IGRA, to improve sensitivity for the individual’s benefit.

The Swiss HIV Cohort Study (SHCS)-team used previously frozen PBMC-stocks from patients with later on clinically diagnosed active TB for Elispot-test, to explore its’ sensitivity in HIV-coinfected patients in combination with TST, i.e. a standard procedure when patients enter the SHCS. However studying TB in a low prevalence country is difficult due to important limitations: First the number of confirmed TB cases is low in relation to frozen PBMC-stocks, indicating an unfavorable cost-benefit analysis. Moreover low case numbers may cause difficulties in reasonable statistical calculations. May be once, the presented data will be evaluated in context of a large multi-cohort meta-analysis. Therefore it is of major interest to have these data published.

Secondly, though a sophisticated logistics to undergo such studies has been established, including harmonized standard of procedures at many different sites, there still may be many TB-patients who though will not enter the study anyway. E.g. a previous PBMC-stock is naturally missing in late presenting HIV-patients with coincidentally diagnosed TB-disease.

Another problem of this study was a relatively high number of indeterminate test results. These results are useless for doctors and patients as they display problems with the test. The reason for this problem remains unknown for the reviewer of this work, though some considerations were given from authors.

**Level of interest:** An article of outstanding merit and interest in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a
statistician.

Declaration of competing interests:
I declare that I have no competing interests