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Prevalence and predictors of tuberculosis among adults with newly diagnosed HIV/AIDS

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Background: Tuberculosis and HIV co-infection not only presents a challenge in diagnosis and therapy but also constitutes a high burden on healthcare systems. A survey was designed to study the prevalence of and risk factors for tuberculosis among antiretroviral-naive HIV-infected adults.

Methods & Materials: A cross-sectional study was conducted among 2866 HIV patients from 10 provinces in China during 2009 to 2010. Clinical and laboratory investigations including chest X-ray, acid fast staining and culture were used to identify tuberculosis cases. Blood samples were collected to determine CD4 + lymphocyte count. A structured questionnaire was used to collect socio-demographic characteristics of study subjects. Factors associated with the presence of tuberculosis were analysed by logistic regression.

Results: Among the 2866 patients, 75.3% were male. Median age was 40 years. 29.8% had tuberculosis, 23.0%

had pulmonary tuberculosis and 11.9% had extrapulmonary tuberculosis. The prevalences of smear-positive pulmonary tuberculosis and of culture-positive pulmonary tuberculosis were 11.8% and 17.2% , respectively. Tuberculosis was more prevalent among men, ethnic minority patients, patients with CD4 count of <200/mm3, and patients who were < 50 years of age. The prevalence of tuberculosis differed significantly according to province and HIV transmission route. Tuberculosis was more common in patients with fever, cough, night sweats, fatigue, weight loss, loss of appetite, abnormal pulmonary imaging findings, and history of tuberculosis. In multivariate analysis, having been diagnosed in provinces Henan (OR = 46.863), Jiangxi (OR = 8.103), Shanghai (OR = 2.273) and Xinjiang(OR = 25.451), male sex (OR = 1.333), ethnic minority (OR = 1.620), lower CD4 count (OR = 1.382), abnormal pulmonary imaging (OR = 3.539), fever (OR = 3.947), cough (OR = 2.223), night sweats (OR = 4.461), weight loss (OR = 1.830), and history of tuberculosis (OR = 3.712) were associated with increased adjusted odds of tuberculosis among HIV patients.

Conclusion: Tuberculosis is highly prevalent among Chinese adults with newly diagnosed HIV/AIDS. Geographical areas, male sex, ethnic minority, lower CD4 count, having abnormal pulmonary imaging findings, history of tuberculosis, and presenting with non-specific symptoms including fever, cough, night sweats or weight loss were found to be the predicting factors for tuberculosis among HIV-infected patients.

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Molecular characterization of mycobacterium tuberculosis strains isolated in India

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Background: Genotypic analyses of *Mycobacterium tuberculosis* are essential in understanding its epidemiology and transmission in a region. Spoligotyping and 24 Loci MIRU-VNTR are widely used PCR based rapid methods for genotyping *M. tuberculosis* complex (MTB) strains. Only few in-depth analyses of the population structure of MTB is known from India. In this study we executed genotyping of *M. tuberculosis* complex clinical isolates from different geographical regions of India.

Methods & Materials: A total of 628 *M. tuberculosis* isolates were collected from 9 different locations of India viz: New Delhi (n=64,10.2%); Agra (n=59,9.4%); Punjab (n=61,9.7%); Mumbai (n=112,17.8%); Nagpur (n=52,8.3%); Hyderabad (n=94,15%); Chennai (n=50,8%); Kolkata (n=75,12%), and Assam (n=61,9.7%). All the isolates were subjected to Spoligotyping and 24 loci MIRU-VNTR and their patterns were analysed using SIT_VIT WEB2 and MIRU-VNTR plus respectively. Clustering and diversity analysis (Huner-Gaston Diversity Index) were also performed.

Results: Spoligotyping analysis detected 102 distinct spoligo-patterns. A total of 536(85.3%) isolates could be grouped into 85 SITs which matched the pre-existing database. For 34(5.4%) ungrouped isolates 17 new SITs were created, and for the remaining 58(9.2%) isolates no SIT number could be ascertained and these were consid-

ered as 'orphan'. All the 58 orphan strains were analysed using 24 loci MIRU-VNTR and appropriate genotypes were identified. Overall using both techniques, CAS family was predominant, comprising of 253(40.3%) isolates, followed by EAI in 172(27.4%), Beijing in 110(17.5%), Manu in 41(6.5%), T in 31(4.9%), H in 11(1.8%), X in 4 (0.6%), Africanum in 4(0.6%) and Ural in one. Using the HuntereGaston diversity index (HGI), the allelic diversity of the loci MIRU10, MIRU 16, MIRU 23, MIRU27, MIRU31, Mtub04, Mtub21, Mtub30, QUB11b, QUB26 and QUB4156 were highly discriminant.

Conclusion: CAS was most predominant in Northern and western parts of India *viz*: Agra, Delhi, Punjab, Mumbai and Nagpur while EAI was predominant in Chennai, Hyderabad. Highest prevalence of Beijing was found in Assam and Kolkata. Our data clearly demarks the prevalence of specific *M. tuberculosis* genotypes among different geographical regions.

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Interleukin-6: a potential biomarker of the success of tuberculosis treatment

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Background: The present measure of the success of TB treatment is fraught with problems. A cytokine biomarker(s), a qualitative and quantitative reflection of the treatment success, is thus warranted. Because TB treatment is expected to affect macrophage and mycobacteria interactions and, consequently cytokine(s) elaboration, a biomarker(s) seems crucial to assess its success.

Methods & Materials: We studied the effect of anti-TB drugs isoniazid (INH), rifampicin (RIF), streptomycin (STP) and ethambutol (EMB) on IL-1β, IL-6, IL-10, IL-12 p40 and IL-12 p70 elaboration by mouse peritoneal macrophages (PMs) infected with *M. tuberculosis* H37Rv for 6 h, 24 h, 4 days and 7 days, *in vitro*, by using a multiplex suspension cytokine array system.

Results: INH, at 6 h, at 0.4 μg/ml (MIC: 0.2 μg/ml) and not at 0.1 and 0.2 μg/ml, and at 24 h and on D 4 and D 7, at all the tested concentrations, significantly ($p < 0.001$) suppressed IL-6 elaboration. RIF, at 6 h, lacked any effect on IL-6 elaboration at 0.4 μg/ml (MIC: 0.8 μg/ml), whereas at 0.8 and 1.6 μg/ml, and at all the tested concentrations at 24 h and on D 4 and D 7, significantly ($p < 0.001$) inhibited IL-6 elaboration. STP, at all the time-points, at 2.5 μg/ml (MIC: 5 μg/ml), lacked any effect on IL-6 elaboration; however, at 5 and 10 μg/ml it caused significant ($p < 0.001$) inhibition. Surprisingly, EMB at 4, 8 and 16 μg/ml (MIC: 8 μg/ml) suppressed IL-6 elaboration at all the time-points studied. *M. tuberculosis*-infected untreated controls, in contrast to the uninfected ones, irrespective of the time-points, elaborated significantly ($p < 0.001$) high concentrations of IL-6 (infected controls, 365 ± 30.41–777.5 ± 74.45 pg/ml; uninfected controls, 15.25 ± 1.77–21 ± 1.41 pg/ml) only. Curiously, all the other cytokines (IL-1β, IL-10, IL-12 p40 and IL-12 p70) were unaffected by the drug treatments.

Conclusion: *M. tuberculosis* -infected PMs, *in vitro*, elaborated IL-6 as the only major cytokine, which was significantly inhibited by anti-TB drugs. Therefore, IL-6 can be developed as a potential biomarker or biosignature to assess the success of the treatment of TB.

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Diagnosis of human tuberculosis: identification of new biomarker(s) and biosignature(s)

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Background: Globally, human tuberculosis (TB), continues to be one of the deadliest public health problem, despite some recent ground success. According to Global TB Report 2014 World over, TB is showing a gradual declining trend, and during the period 2000 to 2013, an estimated 37 million lives were saved largely due to improvements in its diagnosis and treatment. Nevertheless, because deaths due to TB are considered preventable, it is only necessary that work must continue to further improve on both these fronts. TB is a chronic inflammatory disease caused by the facultative intra-macrophage pathogen *Mycobacterium tuberculosis*, and their resultant interaction is known to elaborate a wide array of cytokines (stand-alone as biomarkers, and as a group, as biosignatures), which, in turn, are believed to be the reflection of the diseases progression and its status at a particular point in time.

Methods & Materials: We, thus studied the serum levels of interleukin-2 (IL-2), IL-4, IL-6, IL-8, IL-10, tumor necrosis factor-α (TNF-α), GM-CSF and interferon-γ (IFN-γ) in TB patients, at Day 0, after one month, and after six month, by using a multiplex (Bioplex) suspension cytokine array. The standard curves for all the cytokines were generated as per the protocol of the supplier.

Results: Results showed that after six month, only IL-2, IL-4, IL-6, IL-8, TNF-α, GM-CSF and IFN-γ showed a major increase; IL-10 showed the least increase only in a few patients. On the other hand, IL-6, IL-8 and GM-CSF showed a maximum increase (IL-6, 140-fold; IL-8, 180-fold; GM-CSF, 140-fold). The remaining cytokines showed relatively lesser increase (IL-4, 1.1-fold; IL-10, 5-fold; IFN-γ, 80-fold and TNF-α, 65-fold).

Conclusion: We conclude that as stand-alone IL-6, IL-8 and GM-CSF may function as potential biomarkers or together, as a group, may be considered as a biosignature for the diagnosis of TB.

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