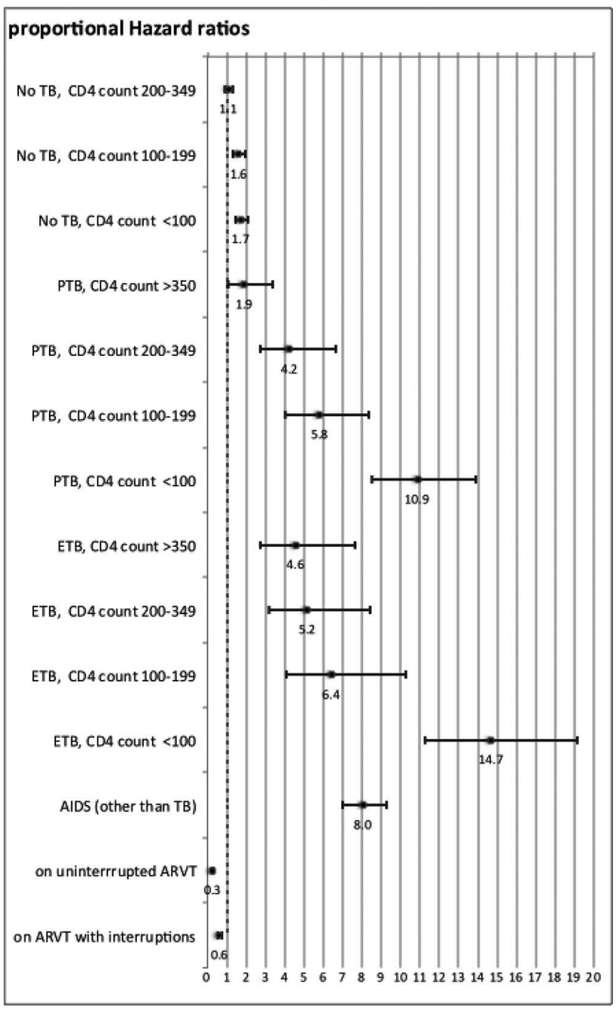
OR relating diabetes to LTBI. Similar results were obtained when the analysis was restricted to contacts.

Conclusions In the current PREDICT cohort, diabetes does not appear to be associated with LTBI after adjustment for age. The relationship between diabetes and TB disease observed elsewhere may reflect an increased risk of disease rather than infection.

S58 TB CO-INFECTION IS ASSOCIATED WITH POOR SURVIVAL AMONG HIV INFECTED PATIENTS IN ENGLAND AND WALES

[1]D Zenner, [1]S Conti, [1]Z Yin, [1]M Kall, [2]M Kruijshaar, [1]B Rice, [1]M Lipman, [3]A Pozniak, [1]I Abubakar, [1]V Delpech; *[1]Centre for Infectious Disease Surveillance and Control Public Health England, London, UK; [2]Erasmus University, Rotterdam, Netherlands; [3]Chelsea and Westminster Hospital, London, UK*

10.1136/thoraxjnl-2013-204457.65



Abstract S58 Figure 1 Multivariable Cox regression model for all cause mortality in persons living with HIV diagnosed in the UK, 2000–2009. Cox regression model for all-cause mortality. There was significant interaction of TB co-infection, CD4 count at diagnosis and site of TB disease–the strata are therefore displayed separately. Dots denote point estimates for hazard ratios for all cause mortality; bars denote 95% confidence intervals. The model was also adjusted for age, sex, region of birth, and probable route of exposure (not displayed here, as effect sizes are moderate and to keep fewer categories). Abbreviations: PTB–pulmonary TB, ETB–extrapulmonary TB, ARVT–Antiretroviral Therapy. The baseline patient is characterised, as a 25–34 year-old UK-born MSM who has never been on ARV, is not TB co-infected and has a CD4 count of 350 or above.

Introduction Tuberculosis (TB) rates in the UK are amongst the highest in Western Europe and HIV-TB co-infection (HIV-TB) contributes significantly to the burden of TB in the UK. Globally, HIV-TB is associated with significant morbidity and mortality, in particular where there is delayed diagnosis. Analysis of setting-specific survival can inform local healthcare policy. Here we report the outcome of individuals diagnosed with HIV in the UK, with particular emphasis on TB co-infection.

Methodology We examined deaths among a retrospective national cohort of adults (15 years +) diagnosed with HIV infection between 2000–2008 linked to the national TB databases and death records from the Office of National Statistics to mid-2010. Hazard ratios (HR) estimates using uni- and multi-variable Cox regression modelling were calculated to compare all-cause and AIDS-specific mortality by key demographic and clinical markers.

Results A total of 1,880 (4.3%) deaths were observed among 44,050 HIV-diagnosed adults during 149,663 person-years of follow-up. 3,188 (7.2%) adults developed TB and HIV-TB cases accounted for 341 (18.1%) of all deaths of whom 270 (79.2%) were late presenters (CD4<200 at HIV diagnosis). One year mortality after HIV diagnosis was 45% overall and greater among HIV-TB cases (54%) and those with low CD4 counts at diagnosis (69% for CD4<50). TB co-infection and a low CD4 count at HIV diagnosis significantly increased the hazard of all-cause mortality. In the fully adjusted model, the highest HR was among adults with extrapulmonary TB and pulmonary TB cases with CD4 count <100 at diagnosis (figure1). The Cox model of AIDS-specific mortality showed similar findings, albeit with increased effect size. Increasing age, female sex, UK country of birth, heterosexual route of exposure to HIV and other AIDS conditions were also associated with poor survival. Antiretroviral therapy (ART) was protective, even if interrupted.

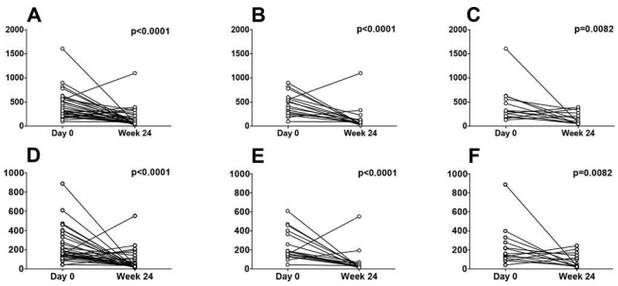
Discussion Despite the availability of effective ART and TB screening and treatment, we observed high death rates among a large national HIV cohort associated with late diagnosis and TB infection. The findings highlight the on-going need for expanded HIV testing and increased TB case finding among HIV diagnosed adults to ensure appropriate and early treatment initiation for both conditions.

S59 DRAMATIC DECLINE IN PLASMA SMALL RNA CONCENTRATION IN HIV-INFECTED AND UNINFECTED INDIVIDUALS RECEIVING ANTI-TUBERCULOSIS THERAPY: A PUTATIVE BIOMARKER OF TREATMENT RESPONSE

I Honeyborne, C Eckold, SH Gillespie, M Lipman, A Pym, TD McHugh; *University College London, London, UK*

10.1136/thoraxjnl-2013-204457.66

Non-coding RNA molecules, particularly miRNA, regulate translation of mRNA and have been found to target expression of genes important in immune response, such as IFN- . Differences in blood transcriptome signatures and differential miRNA expression have been reported to discriminate between uninfected, active and latent tuberculosis. We analysed the ability of small RNA molecules (0–150 nucleotides) in blood plasma to act as biomarkers of tuberculosis treatment response. Total blood



Abstract S59 Figure 1. Concentration of small RNA in blood plasma before (Day 0) and after (week 24) treatment for individuals with active pulmonary tuberculosis and who were culture-negative at week 24 (n = 31): A-C Small RNA concentration (6–150 nucleotides), D-F miRNA concentration (10–40 nucleotides). A and D all individuals, B and E are HIV-1 negative (n = 17) and C and F are co-infected with HIV-1 (n = 14).

plasma small RNA (0–150 nucleotides) concentration was significantly higher ($p < 0.0001$) in 31 individuals before therapy (median 332pg μL^{-1} plasma, range 93–1603pg μL^{-1}) than at the end of therapy at week 24 (median 86pg μL^{-1} plasma, range 16–1098pg μL^{-1}). Expression analysis of small RNA genes revealed that, in 5 tuberculosis-infected HIV-1 negative individuals, 36 of 90 genes (> 2-fold, $p < 0.05$) were upregulated before compared to post-therapy completion. Hsa-miR-19b, 29a, 17–3p, 133a, small RNA concentration and SNORD61 were further tested and this analysis revealed that in 84% of individuals (n = 31) at least one of these biomarkers was upregulated > 2 fold in active tuberculosis. Co-infection with HIV-1 was not found to change the expression of these six tested biomarkers.

S60 RISK FACTORS ASSOCIATED WITH MYCOBACTERIUM TUBERCULOSIS (MTB) INFECTION AND PROGRESSION TO ACTIVE TB DISEASE IN CHILD CONTACTS

N Karnani, S Sridhar, D Connell, A Lalvani; *Imperial College London, London, United Kingdom*

10.1136/thoraxjnl-2013-204457.67

Background Mathematical modelling has shown the most effective strategy to eliminate tuberculosis (TB) worldwide is to address the large burden of latent TB infection (LTBI). Identification of the risk factors which predispose individuals to acquire Mtb infection and those determining risk of progressing from infection to active disease will enable risk stratification for targeted TB interventions.

Objective To identify host, socioeconomic and environmental risk factors for acquiring Mtb infection following exposure to TB and risk factors for progression from infection to active TB disease.

Methods Risk factors associated with infection and progression were investigated in a primary analysis of a well-defined cohort of 965 Turkish household child contacts exposed to smear positive pulmonary TB patients. Risk factors for infection were assessed in study subjects with and without Mtb infection. Mtb infection was defined by interferon gamma-release assay (IGRA) results at two time points–baseline and 6 months–thus creating robust criteria to avoid misclassification of IGRA converters and IGRA reverters. Adjusted odd ratios were estimated using stepwise logistic regression including variables with $p < 0.2$ on univariate regression.

Results In the child cohort passive smoking was found to be an independent risk factor for Mtb infection (OR: 1.52, 95% CI: 1.09 –2.12). Higher household monthly income was an independent protective factor against Mtb infection (OR: 0.55, 95% CI: 0.38 –0.79). Increasing age was associated with a decreased risk of progressing from infection to disease (OR: 0.67, 95% CI: 0.51–0.87). Children exposed to more than 1 TB patient were 8 times more likely to progress to disease (OR: 8.66, 95% CI: 1.54–48.55).

Conclusion Identification of an association between passive exposure to cigarette smoke and acquisition of Mtb infection in children adds new evidence for smoking cessation strategies to be incorporated into TB prevention programmes. To aid TB elimination we therefore advocate an enforcement of stricter tobacco control policies, particularly in regions with a high burden of TB.

S61 SERIAL IGRA TESTING TO IDENTIFY RECENTLY ACQUIRED LTBI IN CONTACTS OF SMEAR POSITIVE PULMONARY TUBERCULOSIS

R Verma, H Patel, H Thuraisingam, G Woltmann, P Haldar; *University Hospitals of Leicester, Leicester, UK*

10.1136/thoraxjnl-2013-204457.68

Introduction We have previously reported prospective data of TB risk in close contacts of tuberculosis with single step interferon gamma release assay (IGRAs) screening 8–12 weeks after index notification and shown a lower positive predictive value of the test in contacts with a higher risk of prior exposure and remote latent tuberculosis infection (LTBI).

We hypothesised that a dynamic change in IGRA response using a two step approach may better identify recent LTBI.

Method Two-step IGRA screening with QuantiFERON TB Gold-In Tube (QFT) was implemented in adult (>16 years) contacts of smear positive pulmonary TB at Leicester. QFT testing was performed as soon as possible after index notification (T1) and if negative repeated after 8–12 weeks (T2). Quantitative QFT values were recorded in all contacts and in those having two tests, the change calculated. Data was mapped to the contacts' risk of remote infection (low, moderate, high) and estimated duration of exposure to the index case based on the reported date of symptoms onset.

Results 397 contacts of 46 smear positive TB cases were identified. 116 children were excluded. 49 adults did not attend for testing (17.4%). 100 contacts (43%) were QFT positive at T1. In regression analysis duration of index symptoms was independently associated with this outcome ($p = 0.001$). ROC curve analysis in subgroups stratified by risk of remote LTBI demonstrated the strongest association to be in the lowest risk group (AUC = 0.93, $p < 0.0001$), with no significant association in the high risk group (AUC = 0.57, $p = 0.404$). 132 contacts were QFT neg at T1 and 109 returned for repeat testing. For the persistently QFT neg group the change in QFT was ± 1 log10 fold between visits. 9 (8.2%) contacts seroconverted. Two subgroups were identified based on the magnitude of change. In 4 contacts the change was within 1 log fold. In the remainder the change was ≥ 2 log fold and all in this subgroup seroconverted with 150 days of symptoms onset in the index.

Conclusions Serial IGRA with ≥ 2 log10 fold change may indicate recent infection. This may be detectable in contacts of index cases with an early diagnosis.