Screen, educate and treat: managing the challenge of TB

S1 HIV-1 INFECTION OF MACROPHAGES MODULATES HOST RESPONSES TO *MYCOBACTERIUM TUBERCULOSIS* TO CONTRIBUTE TO IMMUNOPATHOGENESIS AND VIRAL PROPAGATION

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¹G S Tomlinson, ²P T G Elkington, ¹M Noursadeghi. ¹University College London, London, UK; ²Imperial College, London, UK

Introduction and Objectives Human immunodeficiency virus (HIV)-1 infection increases the risk of active tuberculosis (TB) by 50-fold. The concurrent HIV and TB pandemics therefore represent a major threat to global health. We study the immunopathogenesis of co-infection with a focus on the role of macrophages. These are sentinel cells of the immune system that orchestrate innate and adaptive immune responses, and within the lung, in particular, can host both *Mycobacterium tuberculosis* (MTb) and productive HIV infection. We tested the hypothesis that HIV infection of macrophages modulates host responses to MTb, and contributes to the pathogenesis of co-infection.

Methods Innate immune responses to MTb were assessed in human macrophages with and without productive HIV-1 infection using genome-wide transcriptional profiling. Array data were validated by quantitative PCR of selected genes and Luminex analysis of cell culture supernatants. ELISA and ELISpot assays were used to assess the effects of co-infection on HIV replication and anti-mycobacterial T cell responses.

Results Major gene expression changes assessed by principle component analysis showed that HIV-infected macrophages exhibited attenuated primary transcriptional responses to MTb, but augmented responses at later time points. In keeping with this assessment, we found that MTb stimulation of macrophages induced early IL10 expression, which was attenuated in HIV co-infected cells, and associated with sustained increased expression of pro-inflammatory mediators at later time points. We confirmed the functional relationship between the IL10 response and consequent homeostatic control of inflammatory responses, by complementing deficient IL10 responses in HIV-infected cells to reverse the pro-inflammatory phenotype. We established that exaggerated inflammatory responses in HIV-infected cells were sustained at 72 h, and likely to affect both HIV replication and consequent anti-mycobacterial immune responses. We show that sustained inflammatory responses to MTb are associated with increased HIV replication and have the capacity to alter T cell responses by increasing Th17 polarisation.

Conclusion HIV-1 infection of macrophages attenuates IL10 responses to MTb, and leads to sustained pro-inflammatory responses that support viral propagation and immunopathogenesis of TB.

S2 MULTI-DRUG RESISTANT TUBERCULOSIS (MDR-TB) TREATMENT IN THE UK: A SURVEY OF INJECTABLE USE AND TOXICITY IN PRACTICE

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¹A Sturdy, ²A Goodman, ³R J José, ⁴A Loyse, ⁵M O'Donoghue, ⁵O M Kon, ⁶M J Dedicoat, ⁴T Harrison, ²L John, ³M Lipman, ⁵G Cooke. ¹Imperial College London, London, UK; ²Northwick Park Hospital, London, UK; ³Royal Free Hospital, London, UK; ⁴St Georges Hospital, London, UK; ⁵St Mary's Hospital, Imperial College Healthcare NHS Trust, London, UK; ⁶Heart of England Foundation Trust, Birmingham, UK

Rationale Recent discoveries in human genetics have identified mitochondrial mutations which confer a high risk of sensorineural

deafness in individuals exposed to aminoglycosides. Successful MDR-TB treatment often requires prolonged use of these agents. There are little data from the UK to inform the use of genetic tests within MDR-TB patients. We set out to survey MDR-TB practice in the UK with an emphasis on injectable drug use, ototoxicity and audiological monitoring practice.

Methods Five centres took part in a retrospective study of patients initiating injectable treatment for MDR-TB between 1 January 2004 and 31 December 2009. Data were collected regarding patient characteristics, choice of injectable, methods and frequency of ototoxicity screening and incidence of drug-related complications.

Results Treatment for 50 MDR-TB patients was reviewed. 29/50 (58%) patients received amikacin, 11/50 (22%) capreomycin, 4/50 (8%) streptomycin and 6/50 (12%) more than one injectable. Three centres used amikacin as their preferred injectable, two used capreomycin. Audiological screening for ototoxicity was variable. 21/50 (42%) patients received baseline screening within 2 weeks of starting an injectable. 16/50 (32%) patients went on to have monthly audiograms, with the majority screened more infrequently or if symptoms were reported. 12/50 (24%) patients received no screening at any point. Ototoxicity was defined as a 20 dB loss from baseline on audiogram at one test frequency, or a 10 dB loss at two adjacent frequencies, or in the absence of a baseline result, as two or more frequencies below 20 dB. If no audiograms were available, the definition was symptomatic. 14/50 (28%) of patients experienced ototoxicity, with 9/50 (18%) left with persistent hearing loss. Increased age ($p=0.02$), use of amikacin ($p=0.02$) and decreased renal function on therapy ($p=0.01$) were significantly associated with ototoxicity (see Abstract S2 Table 1). No centre routinely tests for mitochondrial DNA mutations.

Abstract S2 Table 1

	Ototoxicity (%) n = 14	No Ototoxicity (%) n = 36	p-Value univariate
Age (years)	41.3 (SD 14.5)	31.9 (SD 11.2)	0.02
Gender			
Female	4 (28.6)	16 (44.6)	
Male	10 (71.4)	20 (55.6)	0.3
Ethnicity			
Caucasian	4 (28.6)	6 (16.7)	
Asian Indian/Pakistani	2 (14.3)	11 (30.6)	
Asian Chinese	0 (0)	2 (5.6)	
Asian Other	1 (7.1)	5 (13.9)	
Asian African	6 (42.9)	11 (30.6)	
All Other	1 (7.1)	1 (2.8)	0.57
HIV status			
Positive	1 (7.1)	4 (11.1)	
Negative	3 (92.9)	32 (88.9)	0.68
Amikacin at any point			
Yes	13 (92.9)	21 (58.3)	
No	1 (7.1)	15 (41.7)	0.02
Capreomycin at any point			
Yes	2 (14.3)	15 (41.7)	
No	12 (85.7)	21 (58.3)	0.07
Duration of injectable treatment (days)	123.4 (SD 62.1)	115.9 (SD 90.2)	0.77
Total dose of injectable agent (g)	96.3 (SD 54.7)	90.7 (SD 63.1)	0.78
Baseline creatinine ($\mu\text{mol/l}$)	85.9 (SD 52.8)	67.7 (SD 12.9)	0.07
Creatinine increase >44 from baseline at any point			
Yes	5 (35.7)	2 (6.5)	
No	9 (64.3)	29 (93.5)	
Not known	0	5	0.01

Conclusions There is local variation in both choice of injectable agent and in ototoxicity screening practices between the MDR treatment

centres studied. The data suggest capreomycin might be associated with less ototoxicity when compared to amikacin. There are no UK guidelines to inform best practice and better evidence, including clinical and cost-effectiveness studies, is needed to inform the implementation of current technology including genetic testing.

S3 FACTORS FOR SUCCESSFUL TREATMENT COMPLETION AMONG MDR TB CASES IN THE UK

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¹L F A Anderson, ¹S T Tamne, ²J W Watson, ¹I A Abubakar. ¹Health Protection Agency, London, UK; ²Department of Respiratory Medicine, St James University Hospital, Leeds, UK

Background UK guidelines recommend at least 18 months treatment for patients with multi-drug resistant tuberculosis (MDR TB). Prior to 2008, treatment completion was only available for 12 months nationally in the UK, therefore the proportion completing treatment was unknown. There is also a lack of recent guidance for the treatment and management of MDR TB cases in resource rich low TB incidence settings.

Aims To report the treatment outcome at 24 months for MDR TB patients between 2004 and 2007 and examine treatment regimens and management associated with successful outcomes, taking clinical, social and demographic factors into account.

Methods A retrospective cohort study was used to follow-up MDR TB patients at 24 months. Patients were identified using the national surveillance system which contains demographic and clinical characteristics of cases and is matched routinely to reference laboratory data. Questionnaires were sent out to case managers to collect information on outcome of care and associated risk factors for treatment completion.

Results 69.6% (142/204) of patients completed treatment at 24 months and 2.9% (6) of these completed treatment within 12 months. 4.4% (9) were still on treatment, 6.9% (14) had their treatment stopped, 6.9% (14) died, 7.8% (16) were lost to follow-up and 4.4% (9) were transferred overseas. Only 40.3% (77/191) patients started on treatment received directly observed therapy at any time. Treatment with a recommended fluoroquinolone (OR=2.3; 95% CI 1.2 to 4.2, $p<0.000$) or a bacteriostatic (OR 2.86; 95% CI 1.6 to 5.3, $p=0.001$), a change in treatment regimen (OR=2.2; 95% CI 1.2 to 4.0, $p=0.01$) and treatment with four or more effective drugs (OR=2.0; 95% CI 1.1 to 3.8, $p=0.02$) were significantly associated with a successful treatment outcome.

Conclusion The proportion of MDR TB cases completing treatment is similar to cases with drug susceptible disease due to the use of individualised treatment regimens. However, treatment completion still remains below World Health Organization targets.

S4 EVALUATION OF TB PEER EDUCATORS—ESSENTIAL PARTNERS IN METROPOLITAN TB CONTROL

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¹J Hall, ²S Bethell, ²S Hellenen, ¹A Story, ³M Lipman. ¹Find & Treat, Department of Health TB Projects, London, UK; ²Groundswell, London, UK; ³Royal Free Hampstead NHS Trust, London, UK

Background One in six of all notified tuberculosis (TB) cases in London are among homeless people, problem drug and alcohol users and prisoners (hard-to-reach). These groups are at high risk of delayed diagnosis, infectious and drug resistant TB and poor treatment outcomes. The Berlin Declaration (2007) stated that affected communities are essential partners in TB control. While initiatives involving hard-to-reach communities in HIV control have proven effective, evidence to

support their contribution to TB control activities is lacking. We aimed to improve service access and uptake of TB screening among hard-to-reach groups by harnessing the authentic voice and experience of former TB patients from these affected communities.

Method Seven former TB patients with a history of homelessness and drug/alcohol dependence were recruited and trained as peer educators to work alongside TB clinics and a mobile x-ray screening service. Qualitative and quantitative methods were used to evaluate their impact on service access and screening uptake.

Results Peers recruited 3200 hard-to-reach clients at 101 screening sessions resulting in 45 hospital referrals between May 2009 and February 2010. Following TB peer training of homeless shelter hostel workers, screening uptake increased from 44% to 75%. Subsequent structured interviews with service users highlighted the importance of peer educators in raising TB awareness and promoting service access.

Conclusion Our evaluation demonstrated that trained peer educators can improve service access and TB screening uptake in the short and medium term in hard-to-reach groups. The success of this approach argues for greater peer educator involvement in strategies to control metropolitan TB.

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S5 PREVALENCE OF LATENT TUBERCULOSIS INFECTION IN IMMIGRANTS TO THE UK: FINDINGS FROM A MULTI-CENTRE STUDY

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¹M Pareek, ²J P Watson, ³O M Kon, ⁴G Woltmann, ¹A Lalvani. ¹Imperial College London, London, UK; ²Leeds Teaching Hospital NHS Trust, Leeds, UK; ³Imperial College Healthcare NHS Trust, London, UK; ⁴University Hospitals Leicester NHS Trust, Leicester, UK

Background Notifications for tuberculosis (TB) in the United Kingdom (UK) increased by 30% between 1992 and 2007 with over-seas-born migrants accounting for 72% of cases in 2007. Much of this increase is due to the synergy of migration from high-TB burden countries and the reactivation of pre-existing latent TB infection (LTBI). Since 2006, NICE guidance advocates screening for LTBI in all children from countries with a TB incidence $>40/100\,000$ and adults from Sub-Saharan Africa and countries with a TB incidence $>500/100\,000$. The rationale underpinning these guidelines remains unclear particularly as there are little data on the prevalence of LTBI in immigrants to the UK from regions with different TB incidence rates.

Aims To quantify the prevalence of LTBI in immigrants, assess factors associated with IGRA positivity and to determine LTBI yield from current screening thresholds recommended by NICE.

Methods Analysis of data prospectively obtained through IGRA testing (QuantiFERON-Gold/QuantiFERON-Gold-in-tube) of immigrants in three different centres in the UK during 2008–2010. Descriptive analyses were undertaken. Yields at different screening thresholds were calculated. Subsequent univariate and multivariate analyses were undertaken to assess independent factors associated with IGRA positivity; $p<0.05$ considered significant.

Results In total 915 immigrants were screened during the study period. Median age was 26.8 years (interquartile range 22–33), 50.6% were female and 72.5% had previously been BCG vaccinated. 48.9% and 28.5% of migrants screened originated from the Indian Subcontinent and Sub-Saharan Africa, respectively. Overall 911/915 individuals had determinate IGRA results—199 (21.7%) tested positive and 712 (77.8%) tested negative; 4 (0.4%) individuals had indeterminate results. Multivariate analysis revealed that increasing age ($p<0.0001$) and increasing TB incidence of country of origin ($p=0.0014$) were independently associated with IGRA positivity. Applying current NICE guidance resulted in a yield of 76/311 (24.4%) but would miss 61.8% of the immigrant population with LTBI (Abstract S5 Table 1).