HIV INFECTION ALTERS ALVEOLAR MACROPHAGE SUPEROXIDE BURST AND PHAGOCYTIC FUNCTION IN MALAWIAN PATIENTS WITH PULMONARY TUBERCULOSIS.

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Background
Tuberculosis (TB) is the leading cause of death due to an infectious disease worldwide. TB/HIV co-infection is particularly prevalent in sub-Saharan Africa, and is associated with increased rates of recurrent TB after treatment completion. Given the central role of the alveolar macrophage (AM) in the control of TB infection in the lung, we wished to explore the impact of HIV infection on AM innate immune functions in patients with pulmonary TB.

Methods
We recruited 39 adult patients with microbiologically-confirmed (Xpert MTB/RIF or culture-positive) pulmonary TB in Blantyre, Malawi. 16 patients (41%) were HIV-positive. AMs were collected by bronchoalveolar lavage at 2 months (n=33) and 4 months (n=24) into TB treatment. AMs were enriched by adherence onto 6-well plates and their function was assessed using quantitative flow cytometry-based reporter bead assays. In brief, the assays exploit silica beads derivatized with a calibration fluorochrome and the fluorogenic reporter substrate Oxyburst Green SE for superoxide burst or DQ Green BSA for bulk proteolysis. Internalised beads gain fluorescence intensity proportional to the degree of activity in the phagosome.

Results
Bulk proteolytic activity was unchanged between 2 and 4 months, regardless of HIV status. HIV-negative patients had a significant reduction in AM oxidative burst activity ($p=<0.05$) by 4 months, in contrast to HIV-positive patients ($p=0.083$). Phagocytic activity increased in HIV-negative patients by 4 months ($p=<0.05$), but not in the HIV-positive patients ($p=0.38$). Higher superoxide burst activity at 2 months was associated with reduced rates of 2-month sputum culture conversion regardless of HIV status (OR 0.001, 95% CI 0-0.225). AM bulk proteolytic and oxidative burst activity was significantly impaired by a history of ever smoking ($p<0.005$ and $p<0.05$ respectively).

Conclusion
HIV infection modulates AM innate immune functions in pulmonary TB. This may reflect a prolonged pro-inflammatory environment in the lung demonstrated by consistently high superoxide burst activity even at 4 months into TB treatment in co-infected patients. This may be due to persistent cell-free and cell-associated HIV in the lung driving alveolar inflammation. Alterations in the immune environment within the lungs of patients with TB/HIV co-infection may impair control of TB infection, and increase the risk of recurrent TB disease after treatment completion. Future work will explore whether changes in the cytokine microenvironment may explain altered AM function in TB/HIV co-infection.