Improved detection of Leishmania exposure using a whole blood cytokine release assay for interferon-γ and interleukin-2 in Ethiopian people living with HIV

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Background: In people living with HIV (PLWH), impaired T-cell immunity increases the rate of progression from Leishmania infection to visceral leishmaniasis (VL). Current screen-and-treat strategies employ a Leishmania diagnostic battery (Leish-DB) relying on parasite-derived (PCR, KAtex) or antibody-based (rK39-RDT, rK39-ELISA, DAT) methods, all showing suboptimal sensitivity and specificity in PLWH. Whole blood cytokine release assays (CRA) measuring IFN-γ and IL-2 after stimulation with soluble Leishmania antigens (SLA) may complement this test panel and improve detection of Leishmania exposure in PLWH.

Methods: A total of 180 PLWH from the Ethiopian PreLeisH cohort were followed over 21 months and classified as Leishmania unexposed (HIV), with asymptomatic Leishmania exposure (ALHIV), experienced past VL episode (pastVL), VL developers (VL-HIV), and potential asymptomatic superspreaders. Leishmania-specific IFN-γ, IL-2 and IP-10 responses were measured by cytometric bead assay. Baseline and longitudinal analyses were performed, including statetransition and correlation analyses.

Findings: Combining Leish-DB with CRA IFN-γ/ IL-2 achieved complete case detection in the pastVL cohort (50/50; 100%) versus Leish-DB alone (46/50; 92%). For AL-HIV, 76.9% of cases were detected and additional Leishmaniaexposed individuals within the HIV cohort. Positivity over consecutive visits improved in pastVL and AL-HIV cohorts when combining Leish-DB and CRA IFN-γ/IL-2. The latter test decreased to the negative test range up to four months before disease onset in VL developers, and in potential asymptomatic superspreaders.

Interpretation: CRA IFN-γ/IL-2 captures Leishmania-specific cellular responses undetected by conventional diagnostics, enabling more robust surveillance of asymptomatic exposure and transmission in immunocompromised individuals, with potential to predict VL development in PLWH.

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