**S5 table. IRIS with severe morbidity or mortality**

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| **Patient** **(Age)** **(Site)** | **Baseline clinical and laboratory status** | **Preceding ART and other treatment**  | **IRIS event**  | **Presenting signs and symptoms for IRIS** | **HIV VL and CD4 response at time of IRIS** | **Investigations & management of IRIS**  | **Course** |
| 1302 (5.7 years)UKZN | PTB and LN (right axillary and supra-clavicular) TBDrug-sensitive *M.tb* on fine needle aspirate and sputum culture; WAZ -0.31VL log 5.4 copies/mm3CD4 - 10 cells/mm3 | ART day 14Anti-TB therapy and prednisolone day 34 | Paradoxical TB in lung parenchyma and cervical LN  | Fever, tender enlarged supraclavicular lymph node. | CD4 increased to 72 cells/mm3Viral load declined to log 1.9 copies/mm3 | Increased opacities and widened mediastinum on CXRTreated for sepsisPrednisone added | Developed extensive vasculitic skin diseaseDied on day 33 |
| 1228 0.61 yearsSU | PTB: cough and perihilar infiltrates on CXR. WAZ -3.63CD4 count - 2077 cells/mlViral load log 6.8 copies/ml | ART day 13Anti-TB treatment: day 53 | Unmasking CNS TB granulomas(CNS lesions not suspected at baseline) | Complex focal seizure for an hourRing-enhancing lesions in right caudate and left parietal lobe (CT scan) | CD4 count increased to 2192 cells/mlVL reduced to 3.61 log copies/ml | Anti-TB treatment: Eth added; dosage RIF, INH and PZA increased.Prednisone added at 2mg/kg/day | Hospitalized for 8 months.Residual developmental delay. |
| 13035.4 yearsUKZN | Cryptococcal meningitis: blood culture positive X2; CSF positive for CRAG (bloody tap)WAZ -0.86CD4 count - 14 cells/mlViral load log 5.6 copies/ml | ART Day 95CM: AmB for 2 weeks, fluconazole (12 mg/kg/day X weeks, then 6mg/kg dailyAnti-TB treatment: Rif/INH/PZA/EMB | Paradoxical Cryptococcal meningitis  | Inability to walk for 2 days and weight lossCulture and CRAG negative. | CD4 count increased to 106 cells/mlVL reduced to <log 2.1 copies/ mm3 | Repeat CSF: culture and CRAG negative; 26 lymphocytes per mm3.Fluconazole increased to 12mg/kg/day for 4 weeksPrednisolone for 2 weeks | Hospitalized for 11 daysFluconazole at 12mg/kg/day repeated with good response |
| 12551.4 years SU | Bicytopenia (Low hematocrit and platelet count). PTB (culture confirmed on day 16)WAZ -2.34CD4 count - 753 cells/mlVL log 6.55 copies/mlAnti-TB treatment preceded ART by 5 days; CXR unchanged from baseline, no abdominal lymph nodes on abdominal sonar) | ART Day 9Anti-TB treatment: Day 14 | Unmasking CMV Colitis  | Severe bloody diarrhea, shocked, abdominal distension CMV pp65 positive (count – 5 cells). CMV viral load -2722 copies/ml (log 3.43)Abdominal sonar - thickened gall bladder and moderate ascites. | CD4 count decreased to 234 cells/mlHIV VL reduced to log 3.8 copies/ml | GanciclovirPrednisolone | Required intensive care, inotropic support  |
| 12825 monthsSU | HIV encephalopathy. WAZ -1.94CD4 count - 876 cells/mlVL RNA log 7 copies/mlCMV pneumonia – Ganciclovir X 2 weeks until 4 days on ART (CMV viral load log 4.14 after completion) | ART: Day 19Anti-TB treatment: Day 26(TB never confirmed) | Paradoxical CMV colitis and pneumonitis(also BCG IRIS) | Bloody diarrhea and shockRespiratory failureCMV viremia confirmed (log 3.74 copies/ml)CXR suggestive of CMV | CD4 count decreased to 215 cells/mlVL reduced to log 4 copies/mm3 | Ganciclovir | Required intensive care, inotropic support  |
| 1246 8 monthsSU | Suppurative otitis media for 3 months, then right middle lobe pneumonia and meningitis. WAZ 0.2CD4 count – 931 cells/mm3VL log 5.95 copies/mm3  | ART: Day 40ART: Day 8 | Unmasking abdominal TB + biliary obstructionALT 48, AST 79, ALP 1434 GGT 1229, Total bilirubin 144, conjugated 109(Also HPPE IRIS) | Obstructive jaundice and enlarged liver: biopsy showed bridging necrosis suggesting biliary obstruction. TB: strongly positive TST, Mother had pleural effusion & responded to anti-TB treatment: | CD4 count decreased to 435 cells/mm3VL reduced to log 5.59 copies/ mm3  | Anti-TB treatment Prednisone | ART interruptions due to severity of biliary obstructionHospitalized for 6 monthsBile lake seen on MRI, gall bladder destroyed. Porto-jejunostomy successful |
| 1652 1.8 yearsBJMC | WAZ 0.2CD4 count – 3739 cells/mm3Plasma HIV RNA log 5.65 copies/mm3  | Day 53 | Possible unmasking TB granulomas (On basis of response to anti-TB meningitis treatment) | Fever, vomiting, rapid worsening level of consciousness and raised ICP CSF 700 cells (Neutrophils 85%), protein 20mg/dl, glucose 40mg/dlMRI – multiple ring-enhancing lesions and lepto-meningeal enhancement suggesting TB granulomas | CD4 count decreased to 2403 cells/mm3VL reduced to log 2.15 copies/ mm3 | CSF culture –ve for TB, fungi, CRAGCSF PCR negative for HSV, serology negative for HSV 1 and 2.Antibody negative for toxoplasmosis in serum and CSF, Serum negative for cysticercosis. Rapid malaria antigen test negativeAll TB studies negative including repeat Mantoux at Week 24 (day 136) | ICU admission. SeizuresResidual hemiparesis Anti-TBM\* treatment initiated after 7 days in ICU followed by improvement |

PTB – pulmonary tuberculosis; WAZ – weight for age Z-score; Ethionamide Eth; Isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA); LN- lymph nodes; CXR – chest radiograph; AmB – Amphotericin B; CRAG – cryptococcal antigen; GER – gastro-esophageal reflux; WAZ – weight for age Z-score; TST – Tuberculin skin test; CXR – chest radiograph; ICU – intensive care unit; ICP – intracranial pressure;

CNS – central nervous system; TBM – tuberculous meningitis; GCV – ganciclovir; MRI – magnetic resonance imaging