Objective
We report two cases of fingolimod associated cryptococcal meningitis while on fingolimod and subsequent central nervous system immune reconstitution inflammatory syndrome (CNS IRIS) after drug discontinuation.

Cases Description
- Two women with fingolimod associated cryptococcal meningitis were identified, ages 40 and 48, with a mean duration of fingolimod treatment of 4.5 years.
- Both patients were lymphopenic at presentation (mean nadir of 207/µL).
- They presented with headache, fever, and altered mental status.
- Their MRIs had leptomeningeal enhancement. Spinal fluid analysis was notable for marked neutrophilic pleocytosis and elevated protein.
- Cryptococcus meningitis was diagnosed based on antigen detection by latex agglutination in CSF and serum, as well as positive CSF culture.
- Both patients required a ventriculoperitoneal shunt for persistent elevation of intracranial pressure.
- They had clinical and radiological deterioration at mean 101 +/- 25 days after discontinuation of fingolimod despite continuing on antifungal therapy.
- They were diagnosed with CNS IRIS and had some improvement with steroids.

Discussion
- Drug-induced lymphopenia and persistent headache were red flags that prompted a spinal tap and testing for opportunistic infections.
- Risk may be higher with longer durations of therapy, older age and lymphopenia.
- Prognosis is poor, and clinical deterioration should be closely monitored for relapsing infection, hydrocephalus, or CNS IRIS.
- Prompt lumbar puncture for atypical symptoms, serum cryptococcal antigen screening, and CD4 monitoring may be needed for earlier identification.
- Discontinuation of fingolimod has led to CNS IRIS.
- The need for cryptococcal antigen surveillance pre-therapy and possibly yearly while on therapy may become important in predicting the risk of infection in the older population.

Selected References