Immune Reconstitution Inflammatory Syndrome (IRIS) and the CNS in HIV-infected persons

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Introduction

- 2.1 million new HIV infections worldwide in 2015 (total: 36.7 million)

CNS infections are a major cause of morbidity and mortality- mainly affecting persons with low CD4 count

- Increased ART availability: reduced mortality

BUT neurological IRIS is a potentially fatal complication of ART

South Africa: 3.4 million people on ART
IRIS in HIV

• Describes a constellation of symptoms and clinical features that occur in previously immune suppressed patients during rapid restoration of immune function in the presence of a pathogen or self-antigen
• Majority of cases associated with infections
• Incidence ranges from 3-39% in unselected pts starting ART
• Mostly during the first 8 weeks after ART initiation
• **Risk factors:**
  - Low CD4 count (50 cells/mm$^3$)/high HIV viral load at starting ART
  - Rapid increase in CD4/decrease in viral load
  - High organism burden at time of starting ART
Forms of IRIS

- Infection not diagnosed/treated
  - ART initiation
  - Clinical deterioration
  - Unmasking (simultaneous) IRIS

- Infection diagnosed and treated
  - Improvement on treatment
  - ART initiation
  - Clinical deterioration
  - Paradoxical (delayed) IRIS

Screen pts prior to ART initiation for opportunistic infections!

Diagnosis of exclusion!
- Drug reaction/toxicity
- Drug-resistant infection
- Other opportunistic infection
- Poor-adherence to treatment
Pathogenesis of IRIS

Risk factors:
- Low CD4 count
- Disseminated OI
- Paucity of inflammatory response to OI (in CM)
- Short duration or suboptimal OI treatment

Possible mechanisms:
- Uncoupling of innate and acquired immunity
- Restoration of exuberant pathogen-specific cellular immune responses
- Defective or delayed regulatory responses

ART initiation

High antigen load

Immune cell dysfunction

Innate immune responses

Acquired immune responses

Excess proinflammatory cytokine activity

Signs: focal
- Localised tissue edema and focal inflammation

Signs: systemic
- Systemic inflammatory response

Symptoms of IRIS

Walker et al. HIV/AIDS- Research and palliative care 2015
<table>
<thead>
<tr>
<th>Underlying Infection</th>
<th>Neurological Manifestation(s)</th>
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<tbody>
<tr>
<td>Cryptococcus neoformans</td>
<td>Meningitis</td>
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<td>Intracerebral cryptocoma/abscess</td>
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<td>Cerebellitis</td>
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<td>Coccidiomycoses</td>
<td>Meningitis</td>
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<td>Candida</td>
<td>Meningitis</td>
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<td>Sporothrix schenckii</td>
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<tr>
<td>Mycobacterium tuberculosis</td>
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<td>Intracerebral tuberculoma</td>
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<td>Radiculopathy</td>
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<td>Epidural abscess</td>
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<tr>
<td>Mycobacterium avium complex</td>
<td>Mass lesion</td>
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<td>Varicella zoster virus</td>
<td>Encephalitis</td>
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<td>Transverse myelitis</td>
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<td>Vasculopathy</td>
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<td>Cytomegalovirus</td>
<td>Ventriculitis</td>
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<td>Vasculitis</td>
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<td>Encephalitis</td>
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<td>Human immunodeficiency virus</td>
<td>Encephalitis/encephalopathy</td>
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<td>Herpes simplex virus</td>
<td>Encephalitis</td>
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<td>JC virus</td>
<td>Progressive multifocal leukoencephalopathy</td>
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<td>Epstein–Barr virus</td>
<td>Cerebral lymphomatoid granulomatosis</td>
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<td>Parvovirus B19</td>
<td>Encephalitis</td>
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<tr>
<td>Toxoplasma</td>
<td>Encephalitis</td>
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</table>
TB-IRIS

• Paradoxical TB-IRIS occurs in 8-54% of TB patients

• **Risk factors:**
  - Short interval between TB treatment and ART
  - Extra-pulmonary TB
  - Lower CD4 at ART initiation
  - Greater drop in VL and rise in CD4 on ART

• Occurs usually within the first few weeks but up to 3 months (INSHI case definition)
Neurological TB-IRIS is common in high HIV/TB settings

279 Paradoxical TB-IRIS suspects

Paradoxical TB-IRIS: 190 patients

Neurological TB-IRIS: 23 patients (12%)

Non-neurological TB-IRIS: 167 patients

Neurological TB-IRIS is common in high HIV/TB settings

75 patients with neurological deterioration during 1st year of ART

- CNS tuberculosis: 27 patients (36%)
- Cryptococcal Meningitis: 18 patients (24%)
- Space occupying lesions: 10 patients (13%)
- Psychosis: 9 patients (12%)

Neurological TB-IRIS: 16 patients (21%)

Asselman V et al. AIDS 2010
Radiological features of neurologic TB-IRIS

- Meningitis and/or tuberculoma
- Radiculomyelitis
- Spondilitis

- Intracerebral and spinal epidural abscesses

Focal pachymeningitis
### CSF *M. tuberculosis* culture positivity

<table>
<thead>
<tr>
<th>Patients</th>
<th>TBM diagnosis</th>
<th>ART start</th>
<th>2 weeks post ART start</th>
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<tbody>
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<td>16</td>
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IRIS 15/16
16 days
(IQR 15-20)

Non IRIS 6/18
(range 4-32 days)

Relative risk of IRIS if culture positive = 9.3, 95% CI 1.4-62.2
P=0.004
CSF Neutrophil count

- **IRIS**
  - P=0.01
  - P<0.0001

- **Non IRIS**
  - P=0.04

**TBM diagnosis**
- Day 0
- Day 14
- 2 weeks post ART/IRIS

**Duration on TB treatment- days**
- 0
- 14
- 28

**ART Start**
- Day 14

**Cells/mm³**
- 0
- 3
- 3
- 2
- 2
- 0
- 0
When to start ART in HIV-associated TBM

Torok et al.
- Double-blinded RCT
- Compared ART started immediately ($\leq 7$ days) vs delayed (2 months) after TB treatment initiation
- Primary outcome: mortality at 9 months follow-up
- 253 Adult TBM patients randomized
- Median CD4 count: $\sim 40$ cells/$\mu$L

Primary outcome

--- Deferred ART
--- Immediate ART

Hazard ratio: 1.12; 95% CI: 0.81–1.55; P=0.50

No survival benefit from early ART

AND

More grade 4 AEs in immediate group (p=0.04)

Management of neurological TB-IRIS

• Prevention:
  - Delay ART to 4-6 weeks in all TBM patients
  - ? Steroids- does not prevent neurological TB-IRIS
  - Maraviroc (CCR5 antagonist) does not prevent TB-IRIS

• Education:
  - Warn patient of potential recurrence of symptoms

• Management:
  - Exclude other causes for deterioration
  - ? Steroids

Corticosteroids

Meintjes et al.

- RCT of prednisone (1.5 mg/kg/day x 2 weeks, then 0.75 mg/kg/day x 2 weeks) compared to placebo
- Adults with mild to moderate TB-IRIS (neurological TB-IRIS excluded)
- Patients who deteriorated on treatment were switched to open-label prednisone
- 110 patients randomized
Outcome

• Prednisone associated with reduced morbidity:
  - Combined end point of days hospitalized plus outpatient therapeutic procedures during 3 months follow-up (3 vs 0, p=0.04)

• No excess of severe adverse events in prednisone arm

Meintjes G et al. AIDS. 2010
Management of Neurological TB-IRIS

• Other drugs:
  - Thalidomide?
    Tuberculomas /neurological TB-IRIS in children
  - Infliximab/Adalimumab?
    Paradoxical CNS TB reaction/ CM-IRIS

• ART continuation as far as possible

Cryptococcal meningitis IRIS

• CM causes 20-25% of AIDS related deaths worldwide
• Incidence of paradoxical CM-IRIS: 8-49% of patients who survive to start ART
• Time to onset: 4-10 weeks
INSHI case definition

Panel 1: Case definition for paradoxical cryptococcal immune reconstitution inflammatory syndrome in patients HIV-1

Antecedent requirements
- Taking antiretroviral therapy
- Cryptococcal disease diagnosed before ART by positive culture or typical clinical features plus positive India ink staining or antigen detection
- Initial clinical response to antifungal therapy with partial or complete resolution of symptoms or signs, fever, or other lesions, or reduction in CSF cryptococcal antigen concentration or quantitative culture

Clinical criteria
- Event occurs within 12 months of ART initiation, reintroduction, or regimen switching after previous failure
- Clinical disease worsening with one of the following inflammatory manifestations of cryptococcosis (see text for possible rarer manifestations):
  - Meningitis
  - Lymphadenopathy
  - Intracranial space-occupying lesion or lesions
  - Multifocal disease
  - Cutaneous or soft-tissue lesions
  - Pneumonitis or pulmonary nodules

Other explanations for clinical deterioration to be excluded
- Non-adherence or suboptimum antifungal therapy, indicated by an increase in quantitative culture or antigen titre, or any positive cryptococcal culture after 3 months of antifungal therapy
- Alternative infection or malignant disease in the affected site
- Failure of ART excluded if possible (eg, failure to achieve $\geq 1$ log$_{10}$ copies/mL decrease in viral load by 8 weeks of ART)

Haddow LJ et al. Lancet Infect Dis 2010
### Risk factors for CM-IRIS

<table>
<thead>
<tr>
<th>Microbiologic</th>
<th>Virologic</th>
<th>Immunologic</th>
<th>Therapeutic</th>
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<tbody>
<tr>
<td><strong>Initial fungal burden</strong></td>
<td>Baseline and IRIS RNA</td>
<td>Baseline CD4 and change with ART</td>
<td>ART timing</td>
</tr>
<tr>
<td>Higher fungal burden/crypt ag titer at CM diagnosis</td>
<td>Higher VL prior to ART initiation</td>
<td>Lower pre-ART CD4 count</td>
<td>Early ART initiation (1-2 weeks)</td>
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<td></td>
<td>- Robust virological response to ART with rapid decline in VL</td>
<td>- Robust immunol response to ART: rapid CD4 increase</td>
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<tr>
<td><strong>Follow-up cryptococcal CSF cultures</strong></td>
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<td>CSF WBC, prot, cytokines</td>
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<tr>
<td>Pos culture end of induction therapy</td>
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<td>- WCC&lt;5 cells/mm³,</td>
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<td>- prot&lt;0.5g/L</td>
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<td></td>
<td></td>
<td>- Low IFN-g, TNF-a (Th1)</td>
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<td>- High IL-4, IL-13 (Th2)</td>
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Pathogenesis

**Th1, Th17 responses to cryptoccocus (IFN-γ, IL-17)**

- Better cryptococcal clearance [22, 61]
  - Decreased risk of CM-IRIS
  - Improved survival [65, 71]

**Th2 response to cryptoccocus (IL-4, IL-13) [35]**

- Dysregulated compartment-specific homeostatic immune response
- Pro-inflammatory monocyte trafficking into CSF

**Decreased**
- Cryptoccocal clearance

**Increased**
- Residual antigen with high fungal burden [13, 19, 21, 65]
- Trafficking of monocytes into CSF [28]
- Increased chemokine expression (CCL2, CCL3) [71, 82]

In absence of CD4 T cells [82]

Primed macrophage

Residual antigen may increase MHC-peptide interactions [59-102]

IL-6 [19, 81]

**CD4 T cell**

- Lymphopenia-induced proliferation of CD4 cells [97, 98]
- ART-induced re-distribution and trafficking of CD4 T cells into CSF [28]
- Naïve to effector T cell phenotype [103]

**Effective T cell responses—predominantly Th1 [19]**

**Effective innate immune responses [82]**

TNF

IL-6

Excessive CNS inflammation with tissue destruction presenting as paradoxical CM-IRIS

CM-IRIS

• Presentation:
  - Recurrent meningitis (usually sterile CSF fungal cultures)± raised ICP
  - ± intracranial cryptococcoma, lymphadenitis, pneumonitis
• Exclusion of antifungal therapy failure (less lymphocytes), other infections
• Mortality: 0%-36%, higher in IRIS compared to non-IRIS patients (36% vs 26%)

McCarthy et al. SAMJ 2007
Imaging CM-IRIS

Post MJD et al Am J Neuroradiol 2013

Cattelan AM et al AIDS 2003
When to start ART in CM

Meintjes et al.
- Double blinded RCT in South Africa and Uganda
- Randomized to ART early (1-2 weeks) vs deferred (5 weeks) after CM diagnosis
- Primary outcome: mortality at 26 weeks
- 177 adults randomized

Meintjes G et al NEJM 2014
Primary outcome

Hazard ratio: 1.73; 95% CI 1.06 to 2.82; P = 0.03).
Management

Suspected case of CM-IRIS recognized

- Perform lumbar puncture
- Measure opening pressure
- Send 14 day fungal CSF culture
- Evaluate other possible infectious etiologies
- Symptomatic treatment
- Consider CT head if available

These recommendations are based on expert opinion as no clinical trials are available and are consistent with the Southern African HIV Clinicians Society Guidelines 2013

Mild Symptoms

- Repeat therapeutic lumbar punctures as needed
- Increase fluconazole to 1,200mg daily
- Close monitoring of clinical status

Fungal culture negative

- Fluconazole reduced to prior dose

Fungal culture positive

- Transition to Amphotericin B for re-induction at least 7-10 days

Severe Symptoms

- Repeat therapeutic lumbar punctures as needed (daily often necessary)
- Start Amphotericin B and Fluconazole 800mg daily
- Close monitoring of clinical status

Fungal culture negative

- Switch Amphotericin B back to Fluconazole if clinically improved and culture negative after 7 days

Fungal culture positive

- Continue Amphotericin B at least 7-10 days

*Ideally corticosteroids are only given once cultures are confirmed negative, but in life-threatening cases with high clinical suspicion of IRIS they may be started immediately

If there is poor symptomatic response to therapeutic LPs, corticosteroids (prednisone 1mg/kg PO daily, or dexamethasone IV) should be considered.
Unmasking CM

- In HIV infected patients:
  
  CD4 < 100 and CrAg titre > 1:8 is associated with frequent unmasking CM
  
  Recommendations: CD4 < 100 and CrAg pos- treat with fluconazole
  
  if any CNS symptoms- LP
Progressive Multifocal Leukoencephalopathy (PML)

- PML caused by JC virus (neurotropic polyoma virus)
- Infects mainly oligodendrocytes (±neurons, granule cells, astrocytes) and results in demyelination, necrosis and cell death due to non-inflammatory lytic reaction
- Consequence of severe deficiency of cellular immune responses due to depletion of MHC Class II restricted CD4 T lymphocytes
JC virus infection

50-70% of adults have antibodies to JC virus

Calabrese LH et al. Nat Rev Rheumatol 2015
PML-IRIS

- Paradoxical PML-IRIS: 18% (may be up to 50%)
- 1 week to 26 months after ART initiation (median: Paradoxical: 4 weeks, Unmasking: 7-8 weeks; minority after 6 months)
  - Wide time range? Relate to redistribution of memory T-cells during first few weeks of immune reconstitution followed by proliferation of naive T cells 1 month to 4 years later
- CD4 at IRIS presentation 150 (range: 21-812 cells/mm³)
- **Risk factors:**
  - Lower pre-ART CD4 count (69 vs 102 cells/mm³)
- **Diagnosis:**
  - Typical MRI
  - JC PCR in CSF (sensitivity 95% off ART, but only 58% on ART)

Pathologically: IRIS pts have +++ more infiltrating CD8 T cells, B cells and plasma cells, higher ratio of CD8: JC infected cells

Thurnher M et al. AJNR 2001
PML-IRIS

• **Mortality:**
  - Paradoxical: 53%, unmasking: 31%
  - Increased mortality: earlier onset of IRIS, higher MRI lesion load, worse disease
  - Increased survival: earlier and more prolonged use of steroids, contrast enhancement on imaging (88% vs 20%)

• **Treatment:**
  - Corticosteroids for patients with cerebral edema
  - ? CCR5 antagonistic drug maraviroc

• **When to start ART:**
  - As soon as possible after PML diagnosis

IRIS without opportunistic infection

• Presentations: encephalitis, demyelinating lesions, new/worsening HAND
• Presents months to years (up to 10 years) after ART initiation

Pathogenesis

- CNS viral escape
- HIV-Tat production with viral inhibition
- Autoimmune response to host antigen

CNS-IRIS in absence of OI

Johnson & Nath Curr Opin HIV AIDS 2014
IRIS without opportunistic infection

• LP: increased protein and lymphocytic pleocytosis (mostly CD8)
• Biopsy: ++CD8 lymphocyte infiltrate in parenchyma, but mostly perivascular regions, astrocytosis, microglial activation, ± demyelination and axonal loss
• May respond to steroids
