Immune Reconstitution Syndrome

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Outline

- TB IRIS
- MAC IRIS
- Cryptococcal IRIS
Issues in using ART during TB therapy

- Identifying patients who would benefit from antiretroviral therapy
- Drug-drug interactions
- Immune reconstitution events
- Overlapping drug side effect profiles - HIV and TB drugs
- Adherence challenge of multidrug therapy for 2 infections
- Coordinating care between TB and HIV care providers
Immune Reconstitution Syndrome

- Immunopathogenesis
- Definition
- Epidemiology
- Diagnosis
- Management
T-Cell Changes During HIV Infection

Healthy HIV+ Late disease

- **Naive cells**
- **Memory cell clones**
- **Effector cell clones**

Effect of Therapy?

Late disease

Post treatment

Naive cells
Memory cell clones
Effector cell clones

Post treatment
Kinetics of CD4+ T cell reconstitution following HAART

- Two-phase process
  - First 2 months, CD4 memory T cells ↑↑
  - “Redistribution phenomenon”
    - Rapid reduction VL obtained with HAART allows recirculation of T cells that were previously recruited in lymphoid tissues at time of active virus replication
    - The steeper ↓ of CD4 before HAART, the steeper early ↑ in CD4 was

Kinetics of CD4+ T cell reconstitution following HAART

• Second phase
  – CD4+ cell expansion slows down after third month of treatment but persists over years
  – Time taken to reach normal / near-normal CD4+ T cell values range from 2 to 6 yr
  – Naïve T cells play major role in long-term phase of the CD4+ T cell reconstitution
  – ORIGIN;
    • Thymic origin
    • Peripheral

Months after HAART

Cells

CD4

Memory T cell

Memory expansion

Naïve T cell

Naïve cell regeneration

Memory cell redistribution

Months after HAART
Immunological outcomes at 96 weeks of GPOvir Z

Weeks after ART

CD4 cell counts (cells/mm$^3$)

T cell function recovery

- CD4+ T cell reactivity to recall Ag from OI (CMV and tuberculin)
  - Before HAART reactivity against CMV and tuberculin were detectable in only 4/20 (20%) tested
  - 12 months after HAART became detectable in up to 60%

Emery S and Lane HC. Current Opinion in Immunology 1997
Immune Reconstitution Syndrome

- Immunopathogenesis
- Definition
- Epidemiology
- Diagnosis
- Management
Immune Reconstitution Syndrome

- Various terminology
  - Immune reconstitution syndrome (IRS)
  - Immune reconstitution inflammatory syndrome (IRIS)
  - Immune restoration disease (IRD)
  - immunorestitution disease
  - immune reconstitution phenomena
- Immune reconstitution syndrome (IRS)
  - Pre-existing partly treated OIs clinically deteriorate (paradoxical worsening)
  - Previously subclinical OIs are “unmasked”
- Immunopathological host inflammatory responses are “switched on”
Two Components of TB IRS

- **Paradoxical TB IRS (Worsening of TB)**
  - TB
  - Response to TB Rx
  - ART
  - Exclude other causes
  - TB IRS

- **Incident TB IRS (Unmasking TB)**
  - ART
  - Exclude active TB
  - TB
  - Incident TB IRS
Immune Reconstitution Syndrome

- Immunopathogenesis
- Definition
- Epidemiology
- Diagnosis
- Management
OI reported in IRIS

- Tuberculosis
- MAC
- Cryptococcus
- Cytomegalovirus (CMV)
- hepatitis B virus
- hepatitis C virus
- Mycobacterium leprae
- Histoplasma capsulatum
- P jiroveci
- varicella-zoster virus
- herpes simplex viruses
- JC virus
- BK virus
- parvovirus B19
- Chlamydia trachomatis

International AIDS Society USA 2005
Non-infectious IRS

- Graves disease
- Sarcoidosis
- Kaposi’s sarcoma
- Guillain-Barré syndrome
- Reiter Syndrome
- Rheumatoid arthritis
- Polymyositis
- Alopecia universalis
Two Components of TB IRS

• Paradoxical TB IRS (Worsening of TB)
  - TB
  - Response to TB Rx
  - ART
  - TB IRS
  - Exclude other causes

• Incident TB IRS (Unmasking TB)
  - ART
  - Exclude active TB
  - TB
  - Incident TB IRS
HAART in HIV/TB Patients

- **Signs:**
  - Fever, increased in size and inflammation of involved LN, new lymphadenopathy, expanding CNS lesions, and worsening of chest X-ray
  - Manifestations may be as subtle as fever and minor lymph node enlargement, or as dramatic as respiratory failure or neurological deterioration

- **Risk factors:**\(^1\)\(^-\)\(^6\)
  - Rapid increased CD4 cells, Higher baseline plasma HIV RNA, rapid fall in initial HIV RNA, short duration between TB treatment and initiation of ART, extrapulmonary TB or disseminated TB

IRIS of TB among co-infected HIV/TB Patients

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Journal/Publication Details</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wendel K, et al.</td>
<td><em>Chest</em> 2001;120;193-197.</td>
<td>11%</td>
</tr>
<tr>
<td>Michailidis, et al.</td>
<td><em>Antivir Ther</em> 2005.</td>
<td>32%</td>
</tr>
</tbody>
</table>
Background. Paradoxical neurologic tuberculosis-associated immune reconstitution inflammatory syndrome (TB-IRIS) is a potentially life-threatening condition that occurs within 3 months after starting combination antiretroviral therapy (ART). The reports in the published literature are anecdotal, and the prevalence and outcomes of neurologic TB-IRIS are unknown.

Methods. We prospectively assessed patients with suspected TB-IRIS from June 2005 through October 2007 at our hospital in Cape Town, South Africa. We defined paradoxical TB-IRIS and paradoxical neurologic TB-IRIS with use of consensus clinical case definitions. We collected data on tuberculosis diagnosis, ART, details of TB-IRIS diagnosis, other opportunistic infections, corticosteroid use, and outcome.

Results. We reviewed 279 patients with suspected TB-IRIS, 54 (19%) of whom had suspected neurologic TB-IRIS, and 225 (81%) of whom had suspected non-neurologic TB-IRIS. Paradoxical TB-IRIS was diagnosed in 190 patients; 23 (12%) of these 190 patients had neurologic TB-IRIS (95% confidence interval, 7%–17%). Eight had meningitis, 7 had tuberculoma, 5 had both tuberculoma and meningitis, and 3 had radiculomyelopathy. Twenty (87%) of the 23 patients with neurologic TB-IRIS required hospital admission (median duration, 12 days; interquartile range, 6–24 days), and 21 (91%) received corticosteroids (median duration, 58 days; interquartile range, 29–86 days). Outcomes 6 months after the initial assessment for neurologic deterioration were as follows: 16 (70%) of the patients were alive (10 of these patients had documented full physical and mental recovery), 3 (13%) were dead, and 4 (17%) were lost to follow-up.

Conclusions. Paradoxical neurologic TB-IRIS accounts for 12% of paradoxical TB-IRIS cases. Neurologic TB-IRIS causes considerable short-term morbidity but has reasonable long-term outcomes. Further research is needed to devise optimal diagnostic and management strategies for patients with tuberculosis who experience neurologic deterioration after starting ART.

Immune Reconstitution Syndrome

- Paradoxical reactions are observed among 2–23% of HIV-ve patients receiving treatment for TB \(^1,^2\)
- Manifestations may be as subtle as fever and minor lymph node enlargement, or as dramatic as respiratory failure or neurological deterioration.
- A prospective series of 104 HIV-ve patients treated for TB in Hong Kong
  - 16 (15.4%) developed a paradoxical reaction after a median of 56 days (20–109 days)\(^3\)

Time to Diagnosis of IRIS after HAART

Time Course of HIV-1 RNA in Response HAART

Onset of Paradoxical Reactions in Thais

Factors: IRIS of Mycobacterial Infection

- Temporal association between starting HAART regimen and subsequent development of clinical phenomena (the majority within 3 months)
- Unusual clinical manifestations
- Unexpected clinical course
- Exclusion of alternative explanations
  - Drug resistance
  - Non-compliance with treatment for OIs
- Evidence of preceding immune restoration
  - Rise in CD4
  - Restoration of cutaneous hypersensitivity to mycobacterial antigens (PPD or MAC antigen)
  - Increased in-vitro T-cell proliferative responses to PPD or MAC antigen
- Histopathological or cytological appearances of unexpectedly florid cell-mediated immune response within tissue samples
- Preceding fall in plasma HIV-1 load, providing evidence of a response to HAART
French 2004 Definition of IRIS

Major criteria

A. Atypical presentation of ‘opportunistic infections or tumours’ in patients responding to antiretroviral therapy (ART).
   Localised disease, eg. lymph nodes, liver, spleen
   Exaggerated inflammatory reaction, eg.
   Severe fever, with exclusion of other causes
   Painful lesions
   Atypical inflammatory response in affected tissues, eg.
   Granulomas, suppurative, necrosis
   Perivascular lymphocytic inflammatory cell infiltrate
   Progression of organ dysfunction or enlargement of pre-existing lesions after definite clinical improvement with pathogen-specific therapy prior to the commencement of ART and exclusion of treatment toxicity and new diagnoses, eg.
   Development or enlargement of cerebral space occupying lesions after treatment for cerebral cryptococcosis or toxoplasmosis
   Progressive pneumonitis or the development of organizing pneumonia after treatment for pulmonary MTB or PCP
   New onset or worsening of uveitis/vitritis after the resolution of CMV retinitis
   Fever and cytopenia after treatment for disseminated MAC
   Enlargement of Kaposi’s sarcoma lesions and subsequent resolution or partial regression without commencement of radiotherapy, systemic chemotherapy or intralesional therapy

B. Decrease in plasma HIV RNA level by $>1 \log_{10}$ copies/mL

Minor criteria

Increased blood CD4 T-cell count after ART.
Increase in an immune response specific to the relevant pathogen, eg. DTH response to mycobacterial antigens
Spontaneous resolution of disease without specific antimicrobial therapy or tumour chemotherapy with continuation of anti-retroviral therapy

2 majors or A + 2 minors

INSHI 2008 Definition of Paradoxical TB-IRIS:

(A) Antecedent requirements (require both)
• Diagnosis of TB
• Initial response to tuberculosis treatment

(B) Clinical criteria
• Onset of TB-IRIS should be within 3 months of ART
• Plus at least 1 major criterion or two minor clinical criteria

Major criteria
• New or enlarging lymph nodes, cold abscesses, or other focal tissue involvement—eg, tuberculous arthritis
• New or worsening radiological features of tuberculosis
• New or worsening CNS tuberculosis
• New or worsening serositis
**INSHI 2008 Definition of TB-IRIS:**

*Minor criteria*
- New or worsening constitutional symptoms such as fever, night sweats, or weight loss
- New or worsening respiratory symptoms such as cough, dyspnoea
- New or worsening abdominal pain accompanied by peritonitis, hepatomegaly, splenomegaly, or abdominal adenopathy

(C) **Alternative explanations must be excluded if possible**
- Anti-TB drug resistance
- Poor adherence
- AnotherOI or neoplasm (it is particularly important to exclude an alternative diagnosis in patients with smear-negative pulmonary tuberculosis and extrapulmonary tuberculosis where the initial tuberculosis diagnosis has not been microbiologically confirmed)
- Drug toxicity or reaction
Relationships among terms between two definitions

- Of 126 patients, median baseline CD4 = 43 cells/µL and VL = 5.9 log10
- 73 (58%) had extrapulmonary/disseminated TB
- 22 (18%) and 21 (17%) fulfilled TB-IRIS criteria by study definition and INSHI-2008 definition, respectively

<table>
<thead>
<tr>
<th>Definition</th>
<th>French 2004 - fulfilled</th>
<th>French 2004 - not fulfilled</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INSHI 2008</strong>Definition-fulfilled</td>
<td>20</td>
<td>1</td>
<td>Positive predictive value = 95% (77% - 99%)</td>
</tr>
<tr>
<td><strong>INSHI 2008</strong>Definition-Not fulfilled</td>
<td>2</td>
<td>103</td>
<td>Negative predictive value = 98% (93 - 99.5%)</td>
</tr>
</tbody>
</table>

Sensitivity = 91% (72% - 98%)
Specificity = 99% (95% - 99.8%)

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Extra-pulmonary TB</td>
<td>9.764</td>
<td>2.195-43.441</td>
</tr>
<tr>
<td>Abdominal tuberculous lymphadenitis</td>
<td>4.059</td>
<td>1.104-14.918</td>
</tr>
<tr>
<td>%CD4 change from baseline &gt;4%</td>
<td>2.213</td>
<td>0.871-5.625</td>
</tr>
<tr>
<td>Baseline HIVRNA &gt;5.0 Log</td>
<td>3.306</td>
<td>0.420-26.024</td>
</tr>
<tr>
<td>Drop in HIV RNA &gt; 3.5 Log</td>
<td>1.458</td>
<td>0.500-4.250</td>
</tr>
</tbody>
</table>

OR = Odds ratio, 95% CI = 95% Confidence interval.

Major Symptoms of Paradoxical Reactions

- Abdominal pain: 4 patients
- Headache: 4 patients
- Diarrhea: 6 patients
- LN enlargement: 12 patients
- Fever: 14 patients

Total 21 cases

### PPD RESULTS AND CD4+ COUNT IN HIV-INFECTED TB PATIENTS ON ANTIRETROVIRALS WHO HAD PARADOXICAL RESPONSES

<table>
<thead>
<tr>
<th>Patient</th>
<th>PPD before ARV (mm induration)</th>
<th>PPD after ARV (mm induration)</th>
<th>Time to PPD Conversion after ARV (wk)</th>
<th>CD4+ Count before ARV (/mm³)</th>
<th>CD4+ Count Within a Month of PPD Conversion (/mm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0</td>
<td>30</td>
<td>20</td>
<td>12</td>
<td>96</td>
</tr>
<tr>
<td>B</td>
<td>0</td>
<td>20</td>
<td>4</td>
<td>80</td>
<td>67</td>
</tr>
<tr>
<td>C</td>
<td>0</td>
<td>0</td>
<td>—</td>
<td>27</td>
<td>—</td>
</tr>
<tr>
<td>D</td>
<td>15</td>
<td>Not done</td>
<td>—</td>
<td>91</td>
<td>—</td>
</tr>
<tr>
<td>E</td>
<td>0</td>
<td>10</td>
<td>2.5</td>
<td>2</td>
<td>32</td>
</tr>
<tr>
<td>F</td>
<td>0</td>
<td>67</td>
<td>9</td>
<td>35</td>
<td>350</td>
</tr>
<tr>
<td>G</td>
<td>0</td>
<td>20</td>
<td>8</td>
<td>75</td>
<td>30</td>
</tr>
<tr>
<td>H</td>
<td>0</td>
<td>7</td>
<td>5</td>
<td>133</td>
<td>110</td>
</tr>
</tbody>
</table>

*Definition of abbreviation: ARV = combination antiretroviral therapy.*
**Immune TB IRS and Whole Blood IFN-γ**

**QuantiFERON-TB Gold In-tube assay: RD1 antigens**
No TB Rx at time of ART

- QuantiFERON-TB Gold In-Tube assays:
  - RD1 antigens
  - PPD

- Paradoxical IRS
  - An early, rapid increase in IFN-γ in response to PPD but not RD1 antigens

- Incident TB on ART
  - Response to RD1 antigens pre-ART and in response to both RD1 antigens and PPD during early ART

Elliot J, et. IAS 2007; Sydney. Abstract MOAB101
Interferon gamma Response to RD1 Ag

Two Components of TB IRS

• Paradoxical TB IRS (Worsening of TB)
  - TB
  | ↓ Response to TB Rx
  |  ↓ ART
  |     ↓ TB IRS
  |       ↓ Exclude other causes

• Incident TB IRS (Unmasking TB)
  - ART
  | ↓ Exclude active TB
  |     ↓ Incident TB IRS
Unmasking IRIS: Timing of Onset

Unmasking IRIS: Intensity of Manifestations

After initiation of ART, there were 81 episodes of major OIs in 61 patients:
- 39 (48.1%) tuberculosis
- 16 (19.8%) CMV retinitis
- 12 (14.8%) MAC infection
- 8 (9.9%) PCP
- 5 (6.2%) cryptococcosis
- 1 (1.2%) penicilliosis

Baseline CD$_4 \leq$50 cells/mm$^3$, male gender, and low body weight were associated with higher incidence of OIs after ART (P <0.05).

AIDS-related OIs after HAART: A Swiss cohort

## Table 1. AIDS-Related Opportunistic Illnesses in individuals Taking Potent Antiretroviral Therapy*

<table>
<thead>
<tr>
<th>Illness</th>
<th>Events Within 6 Months Before Start of Potent Antiretroviral Therapy</th>
<th>Events Within 15 Months After Start of Potent Antiretroviral Therapy</th>
<th>No. (%) Within First 3 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Patients (n = 131)</td>
<td>Incidence per 100 Person-Years†</td>
<td>CD4 at Event, ×10^9/L, Median (Range)</td>
</tr>
<tr>
<td>Esophageal candidiasis</td>
<td>28</td>
<td>3.14</td>
<td>28 (0-194)</td>
</tr>
<tr>
<td>Nontuberculous mycobacteria</td>
<td>16</td>
<td>1.79</td>
<td>16 (0-151)</td>
</tr>
<tr>
<td>Cytomegalovirus disease</td>
<td>20</td>
<td>2.24</td>
<td>28 (0-230)</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>6</td>
<td>0.67</td>
<td>175.5 (13-222)</td>
</tr>
<tr>
<td><em>Mycobacterium tuberculosis</em></td>
<td>7</td>
<td>0.78</td>
<td>6 (3-41)</td>
</tr>
<tr>
<td>Pneumocystis carinii pneumonia</td>
<td>21</td>
<td>2.35</td>
<td>28 (2-460)</td>
</tr>
<tr>
<td>Toxoplasmosis</td>
<td>13</td>
<td>1.45</td>
<td>10 (0-207)</td>
</tr>
<tr>
<td>Kaposi sarcoma</td>
<td>18</td>
<td>2.02</td>
<td>48 (2-292)</td>
</tr>
<tr>
<td>Progressive multifocal leukoencephalopathy</td>
<td>2</td>
<td>0.22</td>
<td>102 (52-152)</td>
</tr>
<tr>
<td>Other</td>
<td>19</td>
<td>2.13</td>
<td>54 (2-250)</td>
</tr>
<tr>
<td>All</td>
<td>150</td>
<td>15.10</td>
<td>26 (0-460)‡</td>
</tr>
</tbody>
</table>

*AIDS indicates acquired immunodeficiency syndrome; †Other, cryptococcosis, isosporiasis, cryptosporidiosis, recurrent bacterial pneumonia, and primary lymphoma of the central nervous system; ‡Calculation of incidence is based on the first event in each patient.

§Missing for 41 events.

|§Missing for 15 events.

AIDS-related OIs after HAART: A Swiss Cohort


Figure 2. Cumulative Probability of Developing an Acquired Immunodeficiency Syndrome (AIDS)-Related Opportunistic Illness (OI) After Starting Potent Antiretroviral Therapy With Stratification by CD4 Cell Count at Baseline

## Rates of Each OIs after HAART

<table>
<thead>
<tr>
<th>OIs</th>
<th>CD4 &lt;50 Group (n = 531)</th>
<th>CD4 &gt;50 Group (n = 262)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuberculosis</td>
<td>33 (6.2%)</td>
<td>6 (2.3%)</td>
<td>0.015</td>
</tr>
<tr>
<td>MAC</td>
<td>12 (2.3%)</td>
<td>0 (0%)*</td>
<td>0.071</td>
</tr>
<tr>
<td>CMV retinitis</td>
<td>16 (3.0%)</td>
<td>4 (1.5%)</td>
<td>0.239</td>
</tr>
<tr>
<td>PCP</td>
<td>6 (1.1%)</td>
<td>2 (0.8%)</td>
<td>0.475</td>
</tr>
<tr>
<td>Penicilliosis</td>
<td>1 (0.2%)</td>
<td>0 (0%)*</td>
<td>0.552</td>
</tr>
<tr>
<td>Cryptococcal meningitis</td>
<td>5 (0.9%)</td>
<td>0 (0%)*</td>
<td>0.670</td>
</tr>
</tbody>
</table>

Table 2. Incidence rate of pulmonary and extrapulmonary tuberculosis in the programmes in Cambodia, Thailand, Kenya, Malawi and Cameroon.

<table>
<thead>
<tr>
<th></th>
<th>Pulmonary tuberculosis (n = 209)</th>
<th>Extrapulmonary tuberculosis (n = 111)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Person-years</td>
</tr>
<tr>
<td>Cambodia</td>
<td>38</td>
<td>501.9</td>
</tr>
<tr>
<td>Thailand</td>
<td>40</td>
<td>382.8</td>
</tr>
<tr>
<td>Kenya</td>
<td>52</td>
<td>295.3</td>
</tr>
<tr>
<td>Malawi</td>
<td>69</td>
<td>482.8</td>
</tr>
<tr>
<td>Cameroon</td>
<td>10</td>
<td>210.2</td>
</tr>
</tbody>
</table>

IR, incidence rate (per 100 person-years); CI, confidence interval.
Impact of TB IRS to Mortality

- Lawn S, et al. (AIDS 2007) reported 10.5% (2 of 19)
- Manosuthi W, et al. (J Infection 2006) reported 9.5% (2 of 21)
Immune Reconstitution Syndrome

- Immunopathogenesis
- Definition
- Epidemiology
- Diagnosis
- Management
Treatment of TB IRIS

To date, randomized clinical trial is still needed!

1. Immune modulation
   - Steroid, NSAIDS

2. ART interruption?
   - HAART is safely continued without need for interruption
   - Life threatening conditions
   - Reintroduction after clinical status improve

3. Surgical intervention
   - drainage
Management of IRIS


  ➢ 109 pts with TB-IRIS were randomized to receive prednisone 1.5 mg/kg/d x 2 weeks then 0.75 mg/kg/d x 2 weeks (N=55) or placebo (N=54)
  • Pts deteriorating after starting study drug could switch to open label prednisone
  • Median age 32; CD4+ 53 cells/µL; 6 pts LTFU in placebo arm
# Management of IRIS

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Prednisone</th>
<th>Placebo</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Hospital days</td>
<td>1</td>
<td>3</td>
<td>0.05</td>
</tr>
<tr>
<td>Cumulative hospital days</td>
<td>282</td>
<td>463</td>
<td>0.05</td>
</tr>
<tr>
<td>Deaths</td>
<td>3</td>
<td>2</td>
<td>0.70</td>
</tr>
<tr>
<td># switched to open label</td>
<td>5</td>
<td>19</td>
<td>0.001</td>
</tr>
<tr>
<td>Steroid AEs</td>
<td>9</td>
<td>3</td>
<td>0.07</td>
</tr>
<tr>
<td>Symptoms improved (5 point score)</td>
<td>----</td>
<td>----</td>
<td>0.003</td>
</tr>
<tr>
<td>Rifampicin resistance</td>
<td>5</td>
<td>7</td>
<td>0.50</td>
</tr>
</tbody>
</table>
MAC IRIS

- 25 of 32 cases (78%) developed symptoms within 1 month after HAART
  - Lymphadenitis with granulomatous inflammation
  - Cutaneous lesion and subcutaneous abscess
  - Endobronchial lesion
  - Small bowel involvement
  - Paravertebral abscesses and psoas abscess
- Negative blood culture
- Absence of wasting

MAC IRIS

- Review 25 papers: described 64 cases
- IRS developed after a median of 4 weeks (IQR 2–8 weeks; range 1–52 weeks) of HAART
- Nadir CD4 count 25 cells/L (IQR 10–39 cells/L) before starting HAART and a median plasma viral load of 3105 RNA copies/mL (range 1103–9106 copies/mL)
- At the time IRD was diagnosed the CD4 lymphocyte count had increased to a median of 140 cells/L (IQR 69–180 cells/L) and the plasma viral load had decreased to below the lower limit

MAC IRIS

MAC: Localized lymphadenopathy

At the time of starting HAART: Minor left hilar and aortopulmonary lymphadenopathy

17 days after HAART: Massive mediastinal lymphadenopathy

MAC before ART

- Disseminated multi-organ infection
- Early symptoms: mild, continuous
- Fever, night sweat, weight loss, diarrhea
- Bacteremia: present

MAC IRS

- Focal infection
- Early symptom: more severe, abrupt
- Fever with lymphadenitis, often painful and may suppurate
- Other localized organs
- Bacteremia: absent
IRIS of Cryptococcosis
IRIS of Cryptococcosis

• a retrospective chart review of 120 patients with cryptococcal disease who initiated combination ART
• 10 patients (11%) developed IRIS within a median of 8 months (range: 2-37 months) after initiating ART
• 3 of 10 patients with IRIS died.
• Risk of developing IRIS
  – Having previously undiagnosed HIV
  – CD4 count <7 cells/µL
  – starting ART within 2 months of cryptococcosis diagnosis

• 52 patients with cryptococcal meningitis received ART.

• median (range) follow-up period of 15.7 (7.9-54.0) m.

• 10 patients (19%) developed cryptococcal IRIS at a timing of 3.0-27.3 months after initiation of ART.

• median time to develop this syndrome was 9.9 (95% CI, 3.9-17.9) m.

• cumulative 25% and 75% occurrence of cryptococcal IRIS were at 8.6 and 21.0 m.

IRIS of Cryptococcosis

Nine of 58 (16%) developed cryptococcal IRS

<table>
<thead>
<tr>
<th>Parameters</th>
<th>At baseline</th>
<th>At day 14</th>
<th>At time of IRS</th>
<th>(P) value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF opening pressure, mmHg, median (IQR)</td>
<td>330 (200-435)</td>
<td>280 (175-403)</td>
<td>460 (250-&gt;600)</td>
<td>0.161</td>
</tr>
<tr>
<td>CSF protein, mg/dl, mean±SD</td>
<td>70.2 ± 53.5</td>
<td>45.7 ± 14.3</td>
<td>102.2 ± 50.1</td>
<td>0.001</td>
</tr>
<tr>
<td>CSF sugar, mg%, mean±SD</td>
<td>33.2 ± 19.1</td>
<td>31.0 ± 10.4</td>
<td>41.3 ± 11.4</td>
<td>0.020</td>
</tr>
<tr>
<td>CSF WBC, cells/mm³, mean±SD</td>
<td>44 ± 99</td>
<td>10 ± 7</td>
<td>42 ± 53</td>
<td>0.112</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>HR</th>
<th>95% CI</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF antigen titer &gt;1:512 at d 14</td>
<td>16.667</td>
<td>1.264-200.000</td>
<td>0.032</td>
</tr>
<tr>
<td>CSF protein at day 14</td>
<td>1.089</td>
<td>1.003-1.182</td>
<td>0.043</td>
</tr>
<tr>
<td>CSF sugar at day 14</td>
<td>1.093</td>
<td>0.981-1.217</td>
<td>0.106</td>
</tr>
<tr>
<td>Baseline log plasma HIV-1 RNA</td>
<td>1.665</td>
<td>0.351-7.897</td>
<td>0.521</td>
</tr>
<tr>
<td>Baseline CD4 cell count</td>
<td>1.006</td>
<td>0.960-1.053</td>
<td>0.814</td>
</tr>
</tbody>
</table>

Table 3. Characteristics of Cerebrospinal Fluid (CSF) Samples in Study of Cryptococcal Immune Reconstitution Inflammatory Syndrome (IRIS)

| Characteristic                                      | Value                     | At time of IRIS diagnosis
data                                |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>At baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opening pressure, median (10th, 90th percentiles)</td>
<td>270 mm CSF (130 mm CSF), 520 mm CSF (225 mm CSF), 600 mm CSF</td>
<td>460 mm CSF (225 mm CSF), 600 mm CSF</td>
</tr>
<tr>
<td>CSF cryptococcal antigen titer, median (10th, 90th percentiles)</td>
<td>1:1024 (1:16, 1:10,000)</td>
<td>1:128 (1:4, 1:256)</td>
</tr>
<tr>
<td>At first culture-negative visit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opening pressure, median (10th, 90th percentiles)</td>
<td>200 mm CSF (100 mm CSF), 330 mm CSF (225 mm CSF), 600 mm CSF</td>
<td>460 mm CSF (225 mm CSF), 600 mm CSF</td>
</tr>
<tr>
<td>Neutrophils, median (10th, 90th percentiles)</td>
<td>0% (0%, 5%)</td>
<td>16% (0%, 60%)</td>
</tr>
<tr>
<td>Lymphocytes, median (10th, 90th percentiles)</td>
<td>92% (0%, 100%)</td>
<td>77% (36%, 95%)</td>
</tr>
</tbody>
</table>

Table 4. Potential Risk Factors for Immune Reconstitution Inflammatory Syndrome

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Odds ratio (90% Wald CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum cryptococcal antigen titer (log₂)</td>
<td>1.37 (1.08–1.74)</td>
</tr>
<tr>
<td>Body mass index</td>
<td>1.14 (1.01–1.29)</td>
</tr>
</tbody>
</table>

Distinguishing IRIS from Relapse of Infection

- Patients with IRIS often develop a higher ICP (45 cm H2O) than those with relapse of infection (31 cm H2O) and typically have negative CSF cultures for Cryptococcus.

- Patients experiencing relapse of cryptococcal meningitis present 5 to 6 months later on average after initial diagnosis of cryptococcosis than do those with IRIS.

- Patients with IRIS-related meningitis have on average
  - lower CrAg titers (1:2048 vs 1:128)
  - higher ICP (31 vs 39 cm H2O)
  - higher CSF WBC counts (12 vs 56 cells)
  - higher glucose levels (39 vs 49 mg/dL)
  - negative CSF cultures for Cryptococcus

- 54 (8.9%) of 601 patients with CM underwent lumbar drain placement
- Median duration of an indwelling lumbar drain = 7 days
- 61 placements in 54 patients, totalling to 473 device-days
- 2nd bacterial infections was 6.3 per 1000 device-days, and 3 (4.9%) of 61 catheters became secondarily infected.

- No difference in median duration of placement between infected and uninfected drains (6 days vs. 7 days, $P = 0.572$)

IRIS associated mycobacteria typically present in inpatients with profound immunodeficiency (CD4 <50) within 3 months after HAART.

Commencement of HAART close to anti-TB treatment is a strong predictor of IRIS.

Patients with AIDS should be carefully screened for mycobacterial infection before commencing HAART.

Adjunctive treatment with corticosteroid or NSAIDS may be necessary.
Avoid prescribing ART within the first 2-3 months following the diagnosis of cryptococcosis.

Closed monitoring few months after initiation of ART.

However, there is no prospective data to support specific recommendations.
<table>
<thead>
<tr>
<th>โรคหรือเชื้อที่ก่อโรค</th>
<th>อาการทางคลินิก</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuberculosis</td>
<td>Paradoxical reaction [Prolong fever (&gt;101.5°F), increasing respiratory</td>
</tr>
<tr>
<td></td>
<td>symptoms, increasing lymphadenopathy, cutaneous lesions, ascites, CXR</td>
</tr>
<tr>
<td></td>
<td>worsening] after initiation of HAART, Tuberculoma, Inflammatory bowel</td>
</tr>
<tr>
<td></td>
<td>perforation, Serositis, Psoas abscess</td>
</tr>
<tr>
<td>MAC and other atypical mycobacteria</td>
<td>Localized lymphadenitis, Necrotizing subcutaneous nodules, Endobronchial</td>
</tr>
<tr>
<td></td>
<td>tumors, Small bowel involvement, Paravertebral abscesses, Osteomyelitis,</td>
</tr>
<tr>
<td></td>
<td>Arthritis, Focal brain lesion, Ileitis</td>
</tr>
<tr>
<td>CMV</td>
<td>CMV retinitis despite rise in CD4+ cells after initiation of HAART, Immune</td>
</tr>
<tr>
<td></td>
<td>recovery vitreitis, Immune recovery uveitis, Early and unusual CMV pneumonitis,</td>
</tr>
<tr>
<td></td>
<td>Pseudotumoral colitis, Adenitis, Encephalitis, Cutaneous ulceration</td>
</tr>
<tr>
<td>Viral hepatitis (B,C)</td>
<td>Worsening hepatitis</td>
</tr>
<tr>
<td>Parvovirus B19</td>
<td>Encephalitis, Worsening anemia</td>
</tr>
<tr>
<td>โรคหรือเชื้อที่เกี่ยวข้อง</td>
<td>อาการทางคลินิก</td>
</tr>
<tr>
<td>------------------------</td>
<td>----------------</td>
</tr>
<tr>
<td>Herpes Simplex</td>
<td>Erosive herpes simplex, Encephalitis</td>
</tr>
<tr>
<td>Varicella zoster virus</td>
<td>Acute retinal necrosis early after effective HAART regimen, Increase rate of shingles after HAART</td>
</tr>
<tr>
<td>Kaposi Sarcoma</td>
<td>Worsening KS lesion with inflammation and edema</td>
</tr>
<tr>
<td>PML</td>
<td>Inflammatory PML variant</td>
</tr>
<tr>
<td>BK virus</td>
<td>Hemorrhagic cystitis</td>
</tr>
<tr>
<td>Cryptococcus</td>
<td>Recurrence of meningitis early after effective HAART, Pulmonary cryptococcosis, Cutaneous cryptococcosis (recurrent abscesses), Necrotizing mediastinal and cervical lymphadenitis, Intracranial cryptococcoma, Intramedullary abscess, Necrotizing pneumonitis</td>
</tr>
<tr>
<td>PCP</td>
<td>Pneumonitis (patchy aveolar or reticulonodular infiltrates)</td>
</tr>
<tr>
<td>Skin yeasts</td>
<td>Folliculitis</td>
</tr>
<tr>
<td>โรคหรือเชื้อก่อโรค</td>
<td>อาการทางคลินิก</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>Worsening of sarcoidosis, Pulmonary infiltrates, Erythrema nodosum,</td>
</tr>
<tr>
<td></td>
<td>Lymphadenopathy, Interstitial nephritis</td>
</tr>
<tr>
<td>Toxoplasmosis</td>
<td>Encephalitis</td>
</tr>
<tr>
<td>Leshmaniasis</td>
<td>Vitreitis, Uveitis, Post-Kala-Azar dermal leshmaniasis</td>
</tr>
<tr>
<td>Bartonella henselae</td>
<td>Granulomatous splenitis</td>
</tr>
<tr>
<td>Leprosy</td>
<td>Leprosy cutaneous lesions</td>
</tr>
<tr>
<td>Microsporidia</td>
<td>Keratoconjunctivitis</td>
</tr>
<tr>
<td>Chlamydia trachomatis</td>
<td>Reiter’s syndrome</td>
</tr>
<tr>
<td>Non infectious etiology</td>
<td>Grave diseases, SLE, Vasculitis, Relapsing Guillain-Barre’s syndrome,</td>
</tr>
<tr>
<td></td>
<td>Rheumatoid arthritis, Polymyositis, Alopecia universalis,</td>
</tr>
<tr>
<td></td>
<td>Cerebral vasculitis, Hyperergic reaction (against tattoos, foreign bodies),</td>
</tr>
<tr>
<td></td>
<td>Pre-eclampsia, Multiple eruptive dermatofibromas, Eruptive cheilitis,</td>
</tr>
<tr>
<td></td>
<td>Peyronie’s disease</td>
</tr>
</tbody>
</table>
### Immune Reconstitution Disease vs. Immunodeficiency Disease

<table>
<thead>
<tr>
<th>Variable</th>
<th>Immune restoration disease</th>
<th>Immunodeficiency disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cause</td>
<td>Immunopathology resulting from the restoration of a “protective” pathogen-specific cellular immune response</td>
<td>Result of failure of “protective” cellular immune responses to control pathogen replication</td>
</tr>
<tr>
<td>HIV RNA level</td>
<td>Always associated with a decrease in the plasma HIV RNA level</td>
<td>Usually associated with a high plasma HIV RNA level</td>
</tr>
<tr>
<td>CD4⁺ T cell count</td>
<td>Usually associated with an increased circulating CD4⁺ T cell count</td>
<td>Associated with a low circulating CD4⁺ T cell count</td>
</tr>
<tr>
<td>Inflammation</td>
<td>Inflammation is atypical in presentation and/or more exaggerated than in immunodeficiency disease (e.g., pain, suppuration, and necrosis)</td>
<td>Inflammatory responses may be blunted</td>
</tr>
<tr>
<td>Testing</td>
<td>Examination of affected tissue or body fluid samples reveals evidence of an immune response (e.g., scarcity of pathogens, infiltrating lymphocytes, and granulomatous inflammation)</td>
<td>Examination of affected tissue or body fluid samples reveals evidence of an impaired immune response (e.g., abundance of pathogens and poorly formed granulomata in mycobacterial disease)</td>
</tr>
<tr>
<td>Pathogen-specific immune response</td>
<td>Pathogen-specific cellular immune responses are increased</td>
<td>“Protective” pathogen-specific immune responses are impaired</td>
</tr>
<tr>
<td>Treatment</td>
<td>The infection may resolve without treatment</td>
<td>Antimicrobial therapy is required to resolve the infection</td>
</tr>
</tbody>
</table>

# Paradoxical IRIS

<table>
<thead>
<tr>
<th></th>
<th>TB IRIS</th>
<th>MAC IRIS</th>
<th>Crypto IRIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset of IRIS after ART</td>
<td>+</td>
<td>++</td>
<td>++ to +++</td>
</tr>
<tr>
<td>Chronicity</td>
<td>+</td>
<td>++</td>
<td>+ to ++</td>
</tr>
<tr>
<td>Frequency</td>
<td>++</td>
<td>+ to ++</td>
<td>+ to ++</td>
</tr>
<tr>
<td>Location</td>
<td>Same site &gt; other sites</td>
<td>Localized &gt; disseminated</td>
<td>Same site &gt; other sites</td>
</tr>
<tr>
<td>Severity and death</td>
<td>+ to ++</td>
<td>0 to +</td>
<td>++</td>
</tr>
<tr>
<td>Dosage of steroid</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Period of treatment</td>
<td>+ to ++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Recurrent rate</td>
<td>+</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Complication or sequelae</td>
<td>+</td>
<td>0 to +</td>
<td>++</td>
</tr>
</tbody>
</table>
THANK YOU