Immune Reconstitution
Inflammatory Syndrome

Basics of Paediatric HIV Prevention and Care

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19 April 2012
Case study: Patient IM

- HIV diagnosed in 2008 age 1 year
  - No CD4 done, not started on ART
- 10 Feb 2012, age 4 years 4 months: Admitted to Red Cross
  - Cough for 2 weeks, weight loss
  - Wasted, generalised lymph nodes, dermatitis
  - CXR: large paratracheal / parahilar lymph nodes
    - Commenced TB treatment
- CD4 16 (5%) VL 277 845 (Log 5.44)
- Abdo ultrasound: Large lymph nodes, abscesses in spleen, granulomas in liver, ?TB vs lymphoma
Case study

• 16/2/12: Induced sputum: Smear positive AFB (scanty)
• 20/2/12: Started ART (ABC/3TC/Kaletra/ritonavir)
• 27/2/12: Pyrexia 38, CRP 112, bands 15%
  – Started piptazobactam / amikacin
  – Blood culture, urine MCS – no growth
  – Systems exam / skin / ENT - NAD
• 3/3/12: Still spiking temps >38
  – Started ertapenem / vancomycin
  – Clinically quite well – out of bed, playing in his cubicle
  – Stopped antibiotics: observed
  – Temp settled over next week
  – Discharged 15/3/12
IRIS

• Clinical deterioration after starting ART
• 2 typical forms:
  • Unmasking IRIS – underlying subclinical infection, flares after starting ART; pathogen usually detectable
  • Paradoxical IRIS – exacerbation / relapse of known, treated infection; antigen-driven immune activation, cultures often sterile
Pathogenesis

• Different forms of exaggerated and dysregulated immune responses
  – Viral aetiology: mostly CD8+ T cells
  – Mycobacterial, fungal aetiology: T-helper cell type 1 (granulomatous)

• Rapid expansion of antigen-specific T cells: pro-inflammatory

• Regulatory T cells not expand at same rate / have reduced functional capacity

• Imbalance in pro-inflammatory / anti-inflammatory cytokines
Immune reconstitution inflammatory syndrome in patients starting antiretroviral therapy for HIV infection: a systematic review and meta-analysis

Monika Müller, Simon Wandel, Robert Colebunders, Suzanna Attia, Hansjakob Furrer, Matthias Egger, for IeDEA Southern and Central Africa

In patients with HIV-1 infection who are starting combination antiretroviral therapy (ART), the incidence of immune reconstitution inflammatory syndrome (IRIS) is not well defined. We did a meta-analysis to establish the incidence and lethality of the syndrome in patients with a range of previously diagnosed opportunistic infections, and examined the relation between occurrence and the degree of immunodeficiency. Systematic review identified 54 cohort studies of 13,103 patients starting ART, of whom 1,699 developed IRIS. We calculated pooled cumulative incidences with 95% credibility intervals (CrI) by Bayesian methods and did a random-effects metaregression to analyse the relation between CD4 cell count and incidence of IRIS. In patients with previously diagnosed AIDS-defining illnesses, IRIS developed in 37.7% (95% CrI 26.6–49.4) of those with cytomegalovirus retinitis, 19.5% (6.7–44.8) of those with cryptococcal meningitis, 15.7% (9.7–24.5) of those with tuberculosis, 16.7% (2.3–50.7) of those with progressive multifocal leukoencephalopathy, and 6.4% (1.2–24.7) of those with Kaposi’s sarcoma, and 12.2% (6.8–19.6) of those with herpes zoster. 16.1% (11.1–22.9) of unselected patients starting ART developed any type of IRIS. 4.5% (2.1–8.6) of patients with any type of IRIS died, 3.2% (0.7–9.2) of those with tuberculosis-associated IRIS died, and 20.8% (5.0–52.7) of those with cryptococcal meningitis died. Metaregression analyses showed that the risk of IRIS is associated with CD4 cell count at the start of ART, with a high risk in patients with fewer than 50 cells per µL. Occurrence of IRIS might therefore be reduced by initiation of ART before immunodeficiency becomes advanced.

Introduction

Several studies have shown that the risk of IRIS is associated with CD4 cell count at the start of ART, with a high risk in patients with fewer than 50 cells per µL. Occurrence of IRIS might therefore be reduced by initiation of ART before immunodeficiency becomes advanced.
IRIS: adults

• Lancet 2010: Meta analysis of 1699 IRIS events in 13 103 patients from 54 cohorts between 1997-2007

Muller Lancet 2010 Immune reconstitution inflammatory syndrome in patients starting antiretroviral therapy for HIV infection: a systematic review and meta-analysis
Diagnostic criteria: adults

- At least 5 different diagnostic criteria in use
- French et al 2004
  - Major criteria:
    - Atypical presentation of opportunistic infection or tumours in patients responding to ART; exaggerated inflammatory reaction, progressive organ dysfunction
    - Decrease viral load by >1 log
  - Minor criteria:
    - Increase CD4 after ART
    - Increased pathogen-specific immune response
  - Spontaneous resolution of disease without specific antimicrobial therapy

- Meintjies et al 2008 (TB-associated IRIS)
  - Antecedents: TB diagnosed, stabilised / improved before starting ART
  - Clinical:
    - New / enlarging lymph nodes, cold abscesses, other focal tissue involvement
    - New / worsening radiology, CNS disease, serositis
  - Exclusion of alternative causes:
    - Failure of TB therapy (adherence / resistance)
    - Other opportunistic infection / neoplasm
    - Reaction to toxic effects of drugs

Muller Lancet 2010 *Immune reconstitution inflammatory syndrome in patients starting antiretroviral therapy for HIV infection: a systematic review and meta-analysis*
1. Marais S Curr HIV AIDS Rep 2009 Management of Patients With the Immune Reconstitution Inflammatory Syndrome
Incidence: adults

- Lancet 2010: Meta analysis of 1699 IRIS events in 13,103 patients from 54 cohorts between 1997-2007
- Incidence stratified by organism, CD4, income

Muller Lancet 2010 Immune reconstitution inflammatory syndrome in patients starting antiretroviral therapy for HIV infection: a systematic review and meta-analysis
Incidence: adults

- Any IRIS: 16.1%
- By organism:
  - CMV uveitis: 37.7%
  - Cryptococcal meningitis: 19.5%
  - Progressive multifocal leucoencephalopathy: 16.7%
  - Tuberculosis: 15.7%
  - Herpes zoster: 12.2%
  - Kaposi’s sarcoma: 6.4%

Muller Lancet 2010 Immune reconstitution inflammatory syndrome in patients starting antiretroviral therapy for HIV infection: a systematic review and meta-analysis
Incidence: adults

- By CD4: Exponential increase as pre-ART CD4 count declined
  - TB IRIS
    - Median CD4<50: in 20.7%
    - Median CD4>50: 17.7%
  - Cryptococcal meningitis:
    - Median CD4<50: in 28.3%
    - Median CD4>50: 2%
  - CMV:
    - Median CD4<50: in 37.7%
    - Median CD4>50: (none)
• By country income:
  – TB / cryptococcal / other IRIS: decreased incidence in lower-income countries
  – Uveitis: equal incidence across all income strata
  – “Diagnostic capacity in resource-limited settings might have restricted complete case ascertainment...”
  – “Inflammatory reactions... are more likely to be recognised in the eye than in other organs”
Paediatric IRIS: Consensus criteria

Table 2: Case definition: consensus criteria for diagnosis of pediatric immune reconstitution inflammatory syndrome

<table>
<thead>
<tr>
<th>Criteria</th>
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<tbody>
<tr>
<td>Evidence of clinical response to ART</td>
<td>Virologic response with $&gt;10^{9}$ copies/ml decrease in HIV RNA (if possible)(^a)</td>
</tr>
<tr>
<td>Clinical deterioration from an infectious or inflammatory condition temporarily related to the initiation of ART</td>
<td>Unmasking IRIS requires a new active diagnosis(^b)</td>
</tr>
<tr>
<td>Symptoms cannot be explained by</td>
<td>For paradoxical TB-IRIS, refer to Table 3 for clinical criteria</td>
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Table 3: Infectious or inflammatory clinical criteria for paradoxical tuberculosis immune reconstitution inflammatory syndrome

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<tr>
<td>Clinical criteria</td>
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<tr>
<td>Major criteria</td>
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<tr>
<td>At least one major clinical criterion or two minor clinical criteria are required</td>
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<tr>
<td>New or enlarging lymph nodes, fistulas, cold abscesses, or other focal tissue involvement.</td>
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<tr>
<td>New or worsening radiological features of TB</td>
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<td>New or worsening central nervous system TB (meningitis or focal neurological deficit)</td>
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<td>New or worsening TB serositis (pleural effusion, ascites, or pericardial effusion) or arthritis</td>
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<tr>
<td>Signs of tuberculin hypersensitivity (e.g., phlyctenular conjunctivitis, erythema nodosum)</td>
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<tr>
<td>Minor criteria</td>
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<td>New or worsening constitutional symptoms such as fever, night sweats or weight loss.</td>
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<td>New or worsening respiratory symptoms such as cough, dyspnea, or stridor</td>
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<td>New or worsening abdominal pain, discomfort, or distension with or without palpable mass including hepatosplenomegaly</td>
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<tr>
<td>Resolution of clinical or radiological findings of the suspected IRIS episode without change in ART, TB treatment, or additional antimicrobial therapy</td>
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<tr>
<td>Supportive observations</td>
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<tr>
<td>Conversion of TST negative to positive in patients receiving TB treatment and ART at time of an IRIS event, or $&gt;5\times$ increase from baseline in interferon release assay (e.g., Quantiferon, ELISPOT)</td>
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<tr>
<td>Opinion</td>
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Paediatric IRIS: Consensus criteria

• Evidence of clinical response to ART
• Clinical deterioration from an infectious or inflammatory agent
• Symptoms not explained by
  – An alternate infection or neoplasm
  – Treatment failure of opportunistic infection
  – Adverse drug reaction
  – Complete non-adherence to ART / TB treatment
Incidence: children

- Depends on CD4, previous infectious organism exposure, age, capacity to diagnose IRIS
- Thailand 2002-2004:\(^1\)
  - 153 children, mean age 7.9 years, mean CD4 5%
  - 32 IRIS events (19%)
  - Median onset 4 weeks (range 2-31 weeks)
- Uganda 2006-2007:\(^2\)
  - 162 children and adolescents, median age 6 years, 70% had CD4<15%
  - 62 IRIS events (38%)
- South Africa 2005-2006:\(^3\)
  - 169 children, median age 8 months,
  - 34 IRIS events (21%)
  - Median onset: 16 days
  - 24/34 (76%) due to BCG

1. Puthanakit Ped Inf Dis J 2006 Immune Reconstitution Syndrome After Highly Active Antiretroviral Therapy in Human Immunodeficiency Virus-Infected Thai Children
2. Orikiriiza AIDS 2010 The clinical pattern, prevalence, and factors associated with immune reconstitution inflammatory syndrome in Ugandan children
Bacillus Calmette-Guérin (BCG) vaccine-induced complications in children treated with highly active antiretroviral therapy
BCG

• RCWMCH 2002-2004:¹
  – 352 children;
  – 21 BCG complications (6%)
  – Median age starting ART: 5 months

• CHER study (early vs deferred ART):²
  – Early ART: 10.9 per 100 person years
  – Deferred ART: 54.3 per 100 person years
  – Low CD4 and high viral load strongest predictors of developing BCG IRIS
  – Lymph node: fistula formation 44%
  – 25% had concurrent TB and BCG

2. Rabie H Int J Tuber Lung Dis 2011 Early antiretroviral treatment reduces risk of bacille Calmette-Guérin immune reconstitution adenitis
Management: BCG IRIS

• BCG IRIS: CHER study\(^1\)
  – No medical / surgical interventions
  – Anti-mycobacterial therapy and/or steroids
  – Incision and drainage only

• No difference in time to resolution
  • Median time to resolution: 4 months

• Consider:
  – Concomitant TB infection
  – Local disease vs dissemination
  – Adverse effects of anti-mycobacterial therapy

1. Rabie H Int J Tuber Lung Dis 2011 *Early antiretroviral treatment reduces risk of bacille Calmette-Guérin immune reconstitution adenitis*
IRIS: other manifestations

• Pulmonary TB, cryptococcal meningitis,
• Also:
  – Non-tuberculous mycobacterial disease
  – Varicella zoster
  – HSV labialis, encephalitis
  – Progressive multifocal leucoencephalopathy
  – Sebhorreic dermatitis
  – CMV pneumonitis
  – Bacteraemia; bacterial sepsis with empyema
Management: principles

• Most cases
  – Continue ART
  – Treat new bacterial / viral infections
  – Close observation

• Severe life-threatening cases:\(^1\)
  – Steroids
  – Prednisone 1.5mg/kg/day for 2 weeks, then 0.75mg/kg/day for 2 weeks
  – Stop ART

1. Marais S Curr HIV AIDS Rep 2009 Management of Patients With the Immune Reconstitution Inflammatory Syndrome
Conclusion

• IRIS: Clinical deterioration after starting ART
• 2 typical forms:
  – Unmasking IRIS
  – Paradoxical IRIS
• Higher incidence in severely immune-compromised children
• Lower incidence after early infant ART initiation
• BCG most common
• Continue ART
• Some will need referral / admission / investigation