Immune Reconstitution Inflammatory Syndrome: A factor in Timing of Initiation of ART

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Outline of Presentation

- What is IRIS
- Types
- Principles behind Case definition of IRIS
- IRIS – cause of early mortality
- IRIS – a factor in optimal timing of ART (PCP, TB, CM)
What is IRIS?

- Aberrant manifestation of immune reconstitution → pathogen specific inflammatory response triggered by:
  - Initiation HAART
  - Re-initiation HAART
  - Change to more active HAART
“Paradoxical” and “Unmasking” IRIS

Paradoxical IRIS:
- An individual with a previously diagnosed OI experiences a clinical deterioration on HAART. ^^

Unmasking IRIS:
- OI appears for the 1st time on HAART in a pt who was not diagnosed with that OI previously
- Sub-clinical or unrecognised infections “unmasked” by pathogen-specific IR.
Incidence

Depends on:
- Level of immunodeficiency at commencing ARVs
- The prevalence of OIs in the population
- Intensity of screening for OIs prior to ART.
- Availability of diagnostic facilities

Incidence in cohort studies:
- 10-40%
- Wide range – reflects characteristics of the population
- Lack of standard case definition
## Clinical Spectrum: Many Pathogens and Syndromes

### Mycobacteria/ bacteria:
- MAC
- MTB
- M. Leprae
- Bartonella
- Chlamydia trachomatis

### Possibly infectious:
- Appendicitis
- GBS
- EF
- PPE
- NHL
- KS

### Viruses:
- CMV
- HSV
- HBV
- HCV
- HZV
- HPV
- JCV
- PB19

### Non-infectious:
- SLE
- Sarcoidosis
- Grave’s disease

### Protozoa:
- Leishmania
- Toxo

### Helminths:
- Schistosoma
- Strongyloides
Clinical features

Almost any organ or system may be affected.

Clinical features depend on:

- Anatomical site affected
- Pathogen involved
- Host-parasite interaction.
Case Definition

- Lack of a widely accepted case definition.
- Difficulty to establish criteria:
  - Diverse clinical presentations
  - Diverse antigens/pathogens
  - Limited value of tests - histology, V/Ls & CD4.
Essentially Components of Case Definition

- Temporal relationship with ART initiation
- Worsening despite appropriate Rx
- Atypical deterioration clinical, histo, imaging
- Absence of other explanation
The central difficulty - differentiating OI d/t residual immunodeficiency [present during early ART] from that d/t immune reconstitution.

Disease process needs to be ‘different' in at least one: location, onset, severity, course.

- Highly subjective
- Require much experience with disease
- Makes the definition specific but less sensitivity.

Timing of onset in relation to commencement of ART is important in making diagnosis.
Why all the interest in IRIS?

- Interesting disease model to study reconstitution and regulation of the human immune system
- Complicates early management of AIDS
  - Morbidity
  - Mortality
IRIS: Contribution to Mortality

- Expect IRIS to be a major problem in ART rollout programs in RLS since the risk factors associated with IRIS are common in RLS.
  - Advanced RVD (Low CD4, high VL, low BMI, low haemoglobin)
  - High prevalence of OIs
  - High pathogen burden
  - Young age (good response to ART)
  - ART naïve (good response to ART)

CID 2009, 49:965
Determinants of Death on ART

Risk of death early in the programme strongly associated with baseline immunodeficiency. ↑ risk of harboring an OI > risk of a negative outcome. Most deaths in first 6/12.
How would IRIS Impact on Timing of ART

- Important contributor to mortality:
  - Consider delaying ART
  - Find balance with risk of ongoing immunodeficiency.

- Not as important a contributor as continued immunodeficiency
  - Consider early initiation:

So what does the literature say about causes of early mortality

What does the IRIS literature say about the contribution of IRIS to mortality
IRIS: uncommonly leads to death

- 7% (4/54) deaths in 1\textsuperscript{st} 3/12 attributed to IRIS
- 3 due to CNS syndromes (CM, TBM, Brain mass).
- Supports view – IRIS generally self-limited, CNS IRIS is of concern

Ugandan Study: addressing cause specific mortality in 1\textsuperscript{st} 3 yrs of ART initiation
Retrospective, limited availability of diagnostic tests, verbal autopsy

CID 2009; 49:965–72
## Prospective Studies on General Cohorts

<table>
<thead>
<tr>
<th>Country</th>
<th>Incidence of IRIS (%)</th>
<th>IRIS deaths relative to total deaths (%)</th>
<th># of all IRIS led to death (%)</th>
<th># on ART died from IRIS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SA₁</td>
<td>116/498 (23.2%)</td>
<td>6/25 (24%)</td>
<td>6/141 (4%)</td>
<td>6/498 (1.2%)</td>
</tr>
<tr>
<td>SA₂</td>
<td>44/423 (10.4%)</td>
<td>2/8 (25%)</td>
<td>2/44 (4.5%)</td>
<td>2/423 (0.5 %)</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>32/186 (17.2%)</td>
<td>3/8 (37%)</td>
<td>3/32 (9%)</td>
<td>3/186 (1.6% )</td>
</tr>
</tbody>
</table>

**IRIS important contributor to mortality!**

**IRIS uncommonly results in death!**

RCT - Optimal timing of ART
ACTG 5164

1st prospective trail - early vs. deferred ART in OIs:

- 2 arms (excluded pts with TB)
- Early: median time to ART 12/7
  142 subjects
- Delayed: median time to ART 45/7
  141 subject

Table 1. Baseline Demographic and Clinical Characteristics by Strategy Arm*.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total</th>
<th>Early</th>
<th>Deferred</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>282</td>
<td>141</td>
<td>141</td>
</tr>
<tr>
<td>Men (%)</td>
<td>241 (85)</td>
<td>120 (85)</td>
<td>121 (86)</td>
</tr>
<tr>
<td>Women (%)</td>
<td>41 (15)</td>
<td>21 (15)</td>
<td>20 (14)</td>
</tr>
<tr>
<td>Black (%)</td>
<td>103 (37)</td>
<td>51 (36)</td>
<td>52 (37)</td>
</tr>
<tr>
<td>Hispanic (%)</td>
<td>101 (36)</td>
<td>52 (37)</td>
<td>49 (35)</td>
</tr>
<tr>
<td>White (%)</td>
<td>64 (23)</td>
<td>29 (21)</td>
<td>35 (25)</td>
</tr>
<tr>
<td>Asian (%)</td>
<td>13 (5)</td>
<td>8 (6)</td>
<td>5 (4)</td>
</tr>
<tr>
<td>Age [median yrs] (IQR)</td>
<td>38 (32–44)</td>
<td>39 (33–44)</td>
<td>38 (32–44)</td>
</tr>
<tr>
<td>IDU never (%)</td>
<td>246 (87)</td>
<td>124 (88)</td>
<td>122 (87)</td>
</tr>
<tr>
<td>CD4 (cells/mm³) Median (IQR)</td>
<td>29 (10–55)</td>
<td>31 (12–54)</td>
<td>28 (10–56)</td>
</tr>
<tr>
<td>HIV RNA (log10) Median (IQR)</td>
<td>5.07 (4.71–5.63)</td>
<td>5.07 (4.74–5.59)</td>
<td>5.08 (4.64–5.64)</td>
</tr>
<tr>
<td>No Prior ART</td>
<td>259 (92)</td>
<td>131 (93)</td>
<td>128 (91)</td>
</tr>
<tr>
<td>PCP</td>
<td>177 (63)</td>
<td>88 (62)</td>
<td>89 (63)</td>
</tr>
<tr>
<td>BI</td>
<td>34 (12)</td>
<td>17 (12)</td>
<td>17 (12)</td>
</tr>
<tr>
<td>Other OI</td>
<td>71 (25)</td>
<td>36 (26)</td>
<td>35 (25)</td>
</tr>
<tr>
<td>Cryptococcus</td>
<td>35 (12)</td>
<td>13 (9)</td>
<td>22 (16)</td>
</tr>
<tr>
<td>Toxoplasmosis</td>
<td>13 (5)</td>
<td>9 (6)</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Histoplasmosis</td>
<td>10 (4)</td>
<td>7 (5)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>CMV</td>
<td>6 (2)</td>
<td>4 (3)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>MAC</td>
<td>6 (2)</td>
<td>3 (2)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Multiple OI/BI (w/in 30 days)</td>
<td>92 (33%)</td>
<td>45 (32%)</td>
<td>47 (33%)</td>
</tr>
</tbody>
</table>

*No statistically significant differences were noted for the various comparisons.
ACTG 5164: Optimal timing of ART

Early Rx ↓ progression to aids/death by ~50% in the first 6 mths.
IRIS in ACTG 5164

IRIS was not significantly different between early (8/141) and deferred grp (12/141).

IRIS developed a median of 33 days

No sig difference in IRIS bet grps on steroids (6%) vs. those not on steroids (9.8%).

Not powered for early ART in CM

For the spectrum of OIs (PCP) seen IRIS should not be a reason to defer ART.
All IRIS is not equal

- Different pathogens
- Different immune responses
- Different organs systems
TB IRIS
Issues with ART & ATT

- Drug interactions
- Drug toxicity - overlapping / synergistic
- High pill burden - adherence
- IRIS - morbidity, mortality, public relations
- Programmatic challenges
# Mortality from TB IRIS

<table>
<thead>
<tr>
<th>Country</th>
<th>Incidence of TB IRIS</th>
<th>Fraction of TB IRIS resulting in deaths</th>
<th>Fraction of deaths d/t TB IRIS</th>
<th>Fraction on ART died from IRIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>S Africa</td>
<td>19/160 (12%)</td>
<td>2/19 (10%)</td>
<td>2/16 (12.5%)</td>
<td>2/160 (1.2%)</td>
</tr>
<tr>
<td>Thailand</td>
<td>21/167 (12.6%)</td>
<td>2/21 (9.5%)</td>
<td>2/5 (40%)</td>
<td>2/167 (1.1%)</td>
</tr>
<tr>
<td>USA</td>
<td>25/137 (18%)</td>
<td>1/25 (4%)</td>
<td>-</td>
<td>1/137 (0.7%)</td>
</tr>
</tbody>
</table>

Primary Objective: Determine the optimal time to initiate ARVs in patients with TB

Inclusion Criteria: Smear positive, on standard TB treatment, HIV positive, CD4 < 500/mm³

Endpoints: 1⁰ all-cause mortality, 2⁰ toxicity, viral load, TB outcomes, IRIS

Randomised to ART during TB treatment and after TB treatment

Analysis as of September 2008

Screened N=1331

Enrolled N=642

Integrated Arm N=429

- Initiated ARVs N=350
  - 94 Completed 24-mo follow-up
  - 203 Continued in follow-up

Sequential Arm N=213

- Initiated ARVs N=100
  - 38 Completed 24-mo follow-up
  - 55 Continued in follow-up

Both Arms similar:
- Age
- Gender
- CD4 (150)
- Viral load
- WHO staging
- Drug Ω
- Prior TB

Safety Monitoring Committee recommended halting sequential arm, continue integrated arms

Kaplan-Meier survival curve

- **Integrated Arm**
- **Sequential Arm**

**Months Post-Randomization**

- **Intensive Phase of TB treatment**
- **Continuation Phase of TB treatment**
- **Post-TB Treatment**

**NEJM:362:697-706.**

- **67d ~2/12**
- **261d ~9/12**
### Main Outcomes on interim Data

<table>
<thead>
<tr>
<th></th>
<th>Integrated arm</th>
<th>Sequential arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths (total)</td>
<td>5.8% (25/429)</td>
<td>12.7% (27/213)</td>
</tr>
<tr>
<td>Deaths (CD4&lt;200)</td>
<td>8.4% (23/273)</td>
<td>15% (21/138)</td>
</tr>
<tr>
<td>Deaths (CD4&gt;200)</td>
<td>1.3% (2/156)</td>
<td>8% (6/75)</td>
</tr>
<tr>
<td>Mortality rate/100 pyr</td>
<td>5.4</td>
<td>12.1</td>
</tr>
</tbody>
</table>

**Hazard Ratio:** 0.44 (95% CI: 0.25 to 0.79); \( p = 0.003 \)

56% lower mortality with integrated TB-HIV treatment

*At time of analysis 83% of Integrated arm and 62% of sequential arm patients initiated ART data provisional*
What about IRIS?

<table>
<thead>
<tr>
<th></th>
<th>Integrated arm</th>
<th>Sequential arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>% IRIS (p&lt;0.05)</td>
<td>12.1% (52/429)</td>
<td>3.8% (8/213)</td>
</tr>
<tr>
<td>IRIS Hospitalization</td>
<td>10/52</td>
<td>0/8</td>
</tr>
<tr>
<td>VL&lt;1000 at 1yr</td>
<td>91.0% (201/221)</td>
<td>80.0% (72/90)</td>
</tr>
<tr>
<td>&gt;95% Adherence</td>
<td>90.4% (311/344)</td>
<td>87.1% (115/132)</td>
</tr>
</tbody>
</table>

No IRIS mortality
4 -steroid treatment

Abstract 36a CROI 2009, courtesy CAPRISA
RCT CAMELIA: Timing of ART in HIV/TB

- ART at 2/52 (n = 332) vs. 8/52 (n = 329) of TB Rx - newly diagnosed PTB, smear positive
- 72% CD4 <50, median VL~ 5.6 log_{10}, BMI 16.7
- 59 deaths in early vs. 90 in late arm (P = .002)
- Risk of death 4% in the “early” arm (p=0.007).
- Late initiation independent predictor of mortality
- IRIS 2-3x more frequent in early arm (P< .0001)
- IRIS not aggressive - relatively easy to manage
- Supports early initiation of ART in HIV/TB

IAC Vienna 2010- Late Breaker presentation
Immediate Versus Deferred ART for HIV-Associated TB Meningitis

Randomized placebo-controlled Trial in Vietnam

Treatment-naive, Suspected TB meningitis (n=253)

- Baseline characteristics
  - 90% male, mostly IDU
  - Advanced HIV disease: mean CD4 < 50 c/mm³, HIV RNA > 100,000 c/mL

Immediate ART (n=127)

Defer ART for two months (n=126)

Primary endpoint: Survival at 9 months

All study subjects received ZDV/3TC + EFV

<table>
<thead>
<tr>
<th>Results</th>
<th>Immediate</th>
<th>Deferred</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality (at 9 mos.)</td>
<td>76 (60%)</td>
<td>70 (56%)</td>
<td>NS</td>
</tr>
<tr>
<td>Virologic Suppression</td>
<td>52%</td>
<td>41%</td>
<td>NS</td>
</tr>
<tr>
<td>Grade 3/4 AE (All)</td>
<td>90%</td>
<td>89%</td>
<td>NS</td>
</tr>
<tr>
<td>Grade 3/4 AE (1st 2 mos.)</td>
<td>86%</td>
<td>75%</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Results support deferred ART in HIV-associated TB meningitis

HAART is critical to the survival of patients with CM

Fig. (3). Kaplan-Meier survival curve demonstrating survival from cryptococcal-related mortality in patients with and without ART.
C-IRIS → High Mortality

<table>
<thead>
<tr>
<th>Country</th>
<th>Incidence of C IRIS</th>
<th>Fraction of C IRIS that died</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>SA</td>
<td>30% (6/18)</td>
<td>83% (5/6)</td>
<td>AIDS 2005, 19:2050</td>
</tr>
<tr>
<td>France</td>
<td>4% (10/239)</td>
<td>30% (3/10)</td>
<td>AIDS 2005, 19:1043</td>
</tr>
<tr>
<td>USA</td>
<td>24% (14/59)</td>
<td>0% (0%)</td>
<td>CID 2005, 40:1049</td>
</tr>
<tr>
<td>Uganda</td>
<td>29% (7/24)</td>
<td>57% (4/7)</td>
<td>CID 2008, 46: 1694</td>
</tr>
<tr>
<td>Multicenter (US, Thai)</td>
<td>13% (13/101)</td>
<td>7.7%(1/13)</td>
<td>CID 2009, 49:931</td>
</tr>
</tbody>
</table>

Risk of C IRIS appears to be higher in RLS
Might be a reflection of local standard of care of CM
RCT of Early vs. deferred ART in CM

- Prospective, open-label, randomized study
- CM Rx 800 mg FLZ/day
- Follow-up 3 years. 1° end-point – mortality
- 28/54 ART ≤72hrs, 26/54 >10/52
- Median CD4 37

3yr mortality - early vs. delayed arm = 88% vs. 54% P<0.006; overall 3yr mortality 73%.

Risk of death ~3x > in early arm – study terminated early by DSMB.

Figure 2. Kaplan-Meier survival estimates by treatment group. Early treatment was associated with increased mortality and a median survival time of 28 days, compared with delayed with median survival time of 637 days ($P = .031$, by log-rank test). ART, antiretroviral therapy.
Early ART in CM

- Higher risk of IRIS
- C IRIS more like to have a negative outcome compared to other IRIS
- ART is important for survival of patients with CM but timing is still unclear.
- Gains made with early ART may be offset by mortality from C IRIS
Conclusion

The timing of ART in the context of an OI – depends:

- On the pathogen
- The organ system involved

PCP – safe to start ART as soon as possible

Smear +ve PTB- ART in the 1st 2/52

Extra pulm TB/CNS- caution – limited data

CM – more circumspect - clinical judgment probably best to defer until completion of consolidation Rx (2/52)
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