ART use in patients with opportunistic infections

Graeme Meintjes
University of Cape Town
GF Jooste Hospital
Incidence of AIDS-defining major opportunistic infections, the HIV Outpatient Study, 1994-2007

Buchacz, AIDS 2010;24:1549
Laboratory-confirmed cryptococcosis in SA

Incidence of cryptococcosis (n=41,666*) vs. number of persons on antiretroviral treatment (ART)** by year, South Africa, 2005-2010

*Complete surveillance audits were conducted from 2008-2010; **ASSA-2003 model
CD4 count at ART initiation, 2005-6

ART-LINC Collaboration of IeDEA

Trop Med Int Health 2008;13:870
Survival after Cryptococcal Meningitis, Uganda

2006-7 in ART era
55% survive to ART
41% survive 6 months

Kambugu, Clin Infect Dis 2008;46:1694
Co-treatment of OI and ART

<table>
<thead>
<tr>
<th>Potential challenges</th>
<th>Potential benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRIS</td>
<td>Reduced HIV progression</td>
</tr>
<tr>
<td>Co-toxicities</td>
<td>Reduced mortality</td>
</tr>
<tr>
<td>Drug-drug interactions</td>
<td>Clearance of OI</td>
</tr>
<tr>
<td>Absorption</td>
<td>Prevent OI recurrence</td>
</tr>
<tr>
<td>Pill burden</td>
<td></td>
</tr>
<tr>
<td>Adherence counseling</td>
<td></td>
</tr>
</tbody>
</table>
When to start ART after recent diagnosis of OI?

Several recent and ongoing clinical trials
Paradoxical immune reconstitution inflammatory syndrome (IRIS)

Recurrent, new or worsening inflammatory features of an OI that is being treated after starting ART

- TB-IRIS lymphadenitis
- Tuberculoma with massive cerebral oedema
- Cryptococcal IRIS with meningo-encephalitis
Pathogenesis of paradoxical IRIS

Recovery of pathogen-specific immune responses and T-cell activation

Inflammatory reactions directed to antigens of opportunistic infection

Recovery of innate immune function

Pro-inflammatory cytokines and chemokines

Defective immune regulatory function
## IRIS meta-analysis

Pooled cumulative incidences as % (95% credibility intervals)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Incidence (%)</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMV retinitis</td>
<td>37.7 (26.6 - 49.4)</td>
<td>-</td>
</tr>
<tr>
<td>Cryptococcal meningitis</td>
<td>19.5 (6.7 - 44.8)</td>
<td>20.8 (5.0 - 52.7)</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>15.7 (9.7 - 24.5)</td>
<td>3.2 (0.7 - 9.2)</td>
</tr>
<tr>
<td>PML</td>
<td>16.7 (2.3 - 50.7)</td>
<td>-</td>
</tr>
</tbody>
</table>

Muller, Lancet Infect Dis 2010;10:251
Neurologic IRIS mortality

• Cryptococcal IRIS
  – Africa: 27-83 %
  – N.American, Europe and SE Asia: 0-20%

• Neurologic TB-IRIS
  – 6-month outcome: 13% died; 17% lost to follow-up

• Progressive Multifocal Leukoencephalopathy (PML) IRIS
  – 19/54 died (35%) in largest series

Haddow Lancet Infect Dis 2010;10:791
Pepper, Clin Infect Dis 2009;48:e96
Tan, Neurology 2009; 72:1458
Prospective study of patients with CM starting ART in Uganda

Cumulative IRIS incidence = 45%
HR for death = 2.3 (95% CI = 1.1 - 5.1)

Major risk factors for IRIS

- Lower baseline CD4 count and higher VL
- Disseminated OI / higher antigen load
- More rapid CD4 and VL response to ART
- Earlier ART initiation after diagnosis of OI

Meintjes, Lancet Infect Dis 2008;8:516
Haddow, Lancet Infect Dis 2010;10:791
Early ART as a risk factor for TB-IRIS

Lawn, AIDS 2007;21:335
Early ART as a risk factor for TB-IRIS

- An association between earlier ART and IRIS has also been shown
  - In several other cohort studies
    - Breen, Thorax 2004;59:704
    - Shelburne, AIDS 2005;19:399
  - In clinical trials of ART timing in TB
    - Blanc, 18th IAS Conference 2010, Abstract THLBB106
    - Abdool Karim, CROI 2011 Abstract 39LB
    - Havlir, CROI 2011 Abstract 38
Early ART as a risk factor for cryptococcal IRIS

- Early retrospective studies identified ART within 4 or 8 weeks as risk factor for IRIS
  
  Shelburne, Clin Infect Dis 2005;40:1049
  Lortholary, AIDS 2005;19:1043
  Bicanic, JAIDS 2009;51:130
  Sungkanuparph, Clin Infect Dis 2009;49:931
  Bicanic, CROI 2011 Abstract 892

- This has not been confirmed in more recent prospective studies
Randomised placebo-controlled trial of prednisone for paradoxical TB-IRIS

- Immediately life-threatening IRIS an exclusion
- 110 patients randomised to prednisone or placebo:
  - 1.5 mg/kg/d for 2 weeks then 0.75mg/kg/d for 2 weeks

<table>
<thead>
<tr>
<th></th>
<th>Placebo n = 55</th>
<th>Prednisone n = 55</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total days hospitalized</td>
<td>463</td>
<td>282</td>
<td>-</td>
</tr>
<tr>
<td>Total number outpatient procedures</td>
<td>28</td>
<td>24</td>
<td>-</td>
</tr>
<tr>
<td>Cumulative primary endpoint (median, IQR)</td>
<td>3 (0-9)</td>
<td>0 (0-3)</td>
<td>0.04</td>
</tr>
<tr>
<td>Death on study</td>
<td>2 (4%)</td>
<td>3 (5%)</td>
<td>0.65</td>
</tr>
<tr>
<td>New WHO stage 4 conditions or invasive bacterial infections</td>
<td>4 (7%)</td>
<td>2 (4%)</td>
<td>0.40</td>
</tr>
</tbody>
</table>
Management of paradoxical IRIS

• **TB-IRIS**
  – Exclude alternative causes for deterioration (especially TB drug resistance)
  – Corticosteroids for life threatening cases
  – In other cases they provide symptomatic benefit
  – Needle aspiration of pus collections

• **Cryptococcal meningitis IRIS**
  – CSF culture to exclude antifungal treatment failure
  – Therapeutic LPs to manage raised intracranial pressure
  – Anecdotal reports of benefit from corticosteroids
• **Pneumocystic pneumonia (PCP) IRIS**
  – Rare, but reports of life-threatening cases requiring ventilation
  – Corticosteroid introduction or dose escalation
    
    Jagannathan, AIDS 2009;23:1794

• **Progressive Multifocal Leukoencephalopathy (PML) IRIS**
  – Role of corticosteroids controversial
  – Deaths and improvements reported on corticosteroids
  – Most compelling indication is cerebral oedema
    
    Tan, Neurology 2009;72:1458
    Berger, Neurology 2009;72:1454

• **Cytomegalovirus (CMV) Immune Recovery Vitritis**
  – Peri-ocular corticosteroids
    
    Henderson, Br J Ophthalmol 1999; 83:540
Randomised strategy trials of ART timing during OI treatment
ACTG A5164 trial
Multicenter: United States and South Africa

Treatable OI or Bacterial infection with CD4 < 200

n = 282
Median CD4 = 29
92% ART naïve

ART within 14 days (Median: 12 days)

Randomised 1:1 (Stratified by infection and CD4 count)

ART deferred until after OI treatment (Median: 45 days)

Followed 48 weeks from study entry

Entry infection
PCP 63%
Cryptococcus 12%
Bacterial 12%
TB excluded

Zolopa, PLoS ONE 2009;4:e5575
Grant, PLoS ONE 2010;5:e11416
Time to AIDS Progression or Death

HR = 0.53
95% CI (0.30 - 0.92)
p = 0.02

Zolopa, PLoS ONE 2009;4:e5575
AIDS progression/death

14.2% in early arm
24.1% in deferred arm

OR = 0.51 (95%CI = 0.27-0.94)

IRIS incidence

<table>
<thead>
<tr>
<th>Early arm</th>
<th>Deferred arm</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.7%</td>
<td>8.5%</td>
<td>0.49</td>
</tr>
</tbody>
</table>

Of patients with PCP starting ART, 4/171 (2%) developed paradoxical PCP-IRIS

Zolopa, PLoS ONE 2009;4:e5575
Grant, PLoS ONE 2010;5:e11416
A5164 Deaths/AIDS Progression by Entry OI or CD4 categories: Log Odds Ratios

Zolopa, PLoS ONE 2009;4:e5575
Cryptococcal Meningitis Trial
Zimbabwe; single-center

First CM diagnosis
ART naïve
n = 54
Median CD4 = 37

Randomised 1:1

Early ART
(within 72 hours)

Follow-up
3 years

Delayed ART
(after 10 weeks)

CM not treated with Amphotericin B
Fluconazole 800mg daily x 10 weeks then 200mg daily
ART: D4T, 3TC, NVP

Makadzange
Clin Infect Dis 2010;50:1532
3 year mortality: 88% (early) vs 54% (delayed) (p < 0.006)

Makadzange, Clin Infect Dis 2010;50:1532
SAPIT trial

Starting Antiretroviral Therapy at Three Points in Tuberculosis

CD4 < 500
PTB Smear positive
N = 642
Median CD4
Integrated 140
Sequential 150

Within 4 weeks of starting TB treatment
Within 4 weeks of completing intensive phase TB treatment
Within 4 weeks of completing TB treatment

INTEGRATED THERAPY
Mean 70 days after TB treatment

SEQUENTIAL THERAPY
Mean 260 days after TB treatment

Follow-up 24 months

Before end of trial, DSMB recommended all patients in SEQUENTIAL THERAPY group be started on ART as soon as possible because of excess mortality in this arm

Karim, NEJM 2010
INTEGRATED versus SEQUENTIAL ARMS

Hazard ratio = 0.44 (95% CI = 0.25-0.79)

Figure 2. Kaplan–Meier Survival Curves.
TB denotes tuberculosis.

25 / 429 died in INTEGRATED THERAPY arm = 5.4 / 100py
27 / 213 died in SEQUENTIAL THERAPY arm = 12.1 /100py
# EARLY versus LATE INTEGRATED ARMS

**Overall: AIDS defining illness or death**

<table>
<thead>
<tr>
<th></th>
<th>Early Integrated arm n = 214</th>
<th>Late Integrated arm n = 215</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of events</td>
<td>18</td>
<td>19</td>
</tr>
<tr>
<td>Person-years</td>
<td>259.4</td>
<td>244.2</td>
</tr>
<tr>
<td>Event rate</td>
<td>6.9</td>
<td>7.8</td>
</tr>
</tbody>
</table>

*(per 100 person-years)*

**Incidence Rate Ratio:** 0.89 (95% CI: 0.44 to 1.79); *p*=0.73

**Similar rates of AIDS defining illness or death**

Salim Karim, Abstract 39LB, CROI 2011
Kaplan-Meier curve for AIDS or death in patients with CD4 <50 cells/mm³

Survival probability

- Early integrated therapy
- Late integrated therapy

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

IRR: 0.32 (0.07-1.13), p=0.06

68% reduction of AIDS / death (p=0.06)
CAMELIA trial
CAMbodian Early vs Late Introduction of Antiretrovirals

CD4 $\leq$ 200
Smear positive
PTB or EPTB
n = 661

Randomised
1:1
Open-label

EARLY
ART 2 weeks
after TB diagnosis

LATE
ART 8 weeks
after TB diagnosis

Follow-up to end
of trial when last
participant completed 50
weeks of study
Median follow up of 27 months

<table>
<thead>
<tr>
<th></th>
<th>EARLY</th>
<th>LATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4 (median)</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>BMI (median)</td>
<td>16.7</td>
<td>16.8</td>
</tr>
<tr>
<td>PTB (%)</td>
<td>69</td>
<td>68</td>
</tr>
<tr>
<td>PTB+EPTB (%)</td>
<td>22</td>
<td>23</td>
</tr>
<tr>
<td>EPTB (%)</td>
<td>9</td>
<td>9</td>
</tr>
</tbody>
</table>

Blanc FX, 18th International AIDS Conference, 2010, Abstract THLBB106
SIGNIFICANT REDUCTION OF MORTALITY IN THE EARLY ARM

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Deaths</th>
<th>Follow-up time*</th>
<th>Mortality rate** (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early arm</td>
<td>332</td>
<td>59</td>
<td>712.4</td>
<td>8.28 (6.42 – 10.69)</td>
<td>0.002</td>
</tr>
<tr>
<td>Late arm</td>
<td>329</td>
<td>90</td>
<td>653.7</td>
<td>13.77 (11.20 – 16.93)</td>
<td></td>
</tr>
</tbody>
</table>

* expressed in person-years

** per 100 person-years

Mortality rate was reduced by 40% when ART started at 2 weeks vs 8 weeks
ACTG 5221 – STRIDE

• Randomized, open-label strategy trial
• HIV+ adults with confirmed or presumed TB
• CD4 < 250
• Two arms
  – Immediate ART (< 2 weeks)
  – Early ART (8-12 weeks)
• ART regimen: TDF/FTC + EFZ

Havlir, Abstract 38, CROI 2011
## RESULTS: Proportion with AIDS/Death

<table>
<thead>
<tr>
<th></th>
<th>Immediate</th>
<th>Early</th>
<th>P (95% CI for difference)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All Subjects</strong></td>
<td>12.9%</td>
<td>16.1%</td>
<td>0.45 (-1.8, 8.1)</td>
</tr>
<tr>
<td><strong>CD4 &lt;50 cells/mm³</strong></td>
<td>15.5%</td>
<td>26.6%</td>
<td>0.02 (1.5, 20.5)</td>
</tr>
<tr>
<td><strong>CD4 ≥50 cells/mm³</strong></td>
<td>11.5%</td>
<td>10.3%</td>
<td>0.67 (-6.7, 4.3)</td>
</tr>
</tbody>
</table>

Havlir, Abstract 38, CROI 2011
ART timing and major outcomes in patients with TB and CD4 < 50

CAMELIA (mortality rate)

STRIDE (percentage)

SAPiT (incidence rate)

Immediate (~2 wk)  Early (~8 wk)

* CAMELIA data represents all patients in trial, majority had CD4 < 50 (median CD4 =25)
CAMELIA, STRIDE and SAPiT trials

Comparing immediate versus early ART:

• TB-IRIS was more frequent in the immediate arm in all 3 studies (2-5 x)
• ART drug switches were more frequent in immediate arm in SAPiT
• Grade 3 or 4 toxicities were not more frequent in the immediate arm in STRIDE
TB Meningitis trial
Vietnam, 2 centers

Torok E, 18th International AIDS Conference, 2010, Abstract xxx

TBM
All CD4
Adjunctive dexamethasone
6-8 weeks
N=253

Immediate ART

Deferred ART
2 months
(Placebo for 2 months then ART)

1:1 Placebo-controlled Stratified by TBM grade

<table>
<thead>
<tr>
<th></th>
<th>Immediate</th>
<th>Deferred</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBM grade 1</td>
<td>31.8%</td>
<td>31.8%</td>
</tr>
<tr>
<td>TBM grade 2</td>
<td>41.3%</td>
<td>36.5%</td>
</tr>
<tr>
<td>TBM grade 3</td>
<td>27%</td>
<td>31.8%</td>
</tr>
<tr>
<td>CD4</td>
<td>39</td>
<td>44</td>
</tr>
</tbody>
</table>

9 months TB treatment
Follow-up 12 months
These data support deferred initiation of ART in HIV-associated TBM, particularly in resource-limited settings.

HR = 1.12 (95% CI = 0.81-1.55)

“These data support deferred initiation of ART in HIV-associated TBM, particularly in resource-limited settings”
When to start ART?

- In general, earlier ART improves outcome particularly in those with the lowest CD4 counts.

- A5164 results support ART 2 weeks after diagnosis of range of non-TB infections.

- In TB, studies favor ART after 2 weeks if CD4 < 50. If CD4 > 50 could defer until 2 months.

- Neurologic OIs are an exception, and timing of ART requires special consideration.
ART timing in cryptococcal meningitis

- Very early ART in Fluconazole-treated patients increased mortality

- A5164 sub-analysis showed trend towards reduced AIDS/death with earlier ART

- IDSA: ART 2-10 weeks
  SA Clinicians Society: 2-4 weeks

- Trial for the Optimal Timing of HIV Therapy After Cryptococcal Meningitis (COAT, NCT01075152)
  - Uganda / South Africa, n = 500
  - ART 1-2 weeks vs 5-6 weeks in Amphotericin B treated patients
  - Primary endpoint: Survival at 26 weeks
ART timing in other CNS OIs

• **TB meningitis**
  – High mortality with immediate ART or ART at 2 months
  – More stage 4 severe AE’s in immediate arm

  Torok, 41st Union World Conference on Lung Health 2010

• **PML**
  – No specific treatment, thus immediate ART
  – 1-year survival in HAART era improved from 0-30% to 38-62%

  Cinque, Lancet Infect Dis 2009;9:625

• **Cerebral toxoplasmosis**
  – Clinical improvement in ~ 90% by day 14
  – IRIS is rare thus no reason to delay ART > 2 weeks

  Luft, NEJM 1993;329:995
  Martin-Blondel, J Neurol Neurosurg Psych 2010
Linkage into care from hospital
Kwazulu-Natal, South Africa

49 participants
Median CD4 = 42
TB 76%
PCP 8%
Chronic diarrhoea 8%
CM 6%
Toxoplasmosis 4%

31% died before ART
45% initiated ART
8% loss to follow-up

Murphy, Int J Tuberc Lung Dis 2010;14:903
Acknowledgements

- Gary Maartens
- Robert Wilkinson
- Katalin Wilkinson
- Suzaan Marais
- Helen van der Plas
- Rene Goliath
- Charlotte Schutz
- Dominique Pepper
- Kevin Rebe
- Molebogeng Rangaka
- Tolu Oni
- Chelsea Morroni

- Tom Harrison
- Joe Jarvis
- Tihana Bicanic
- David Boulware
- Bob Colebunders

SLIDES/INPUT
Andrew Zolopa, Estee Torok, Matthias Egger, Andrew Boulle, Kate Buchacz, Stephen Lawn, Nelesh Govender, Bill Burman