Advanced HIV

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Department of Medicine
(Thanks to Graeme Meintjes for some slides)
Incidence of common OIs in Cape Town

Holmes JAIDS 2006;42:464
In 2015 37% of people starting ART did so at CD4 cell count <200 cells/mm³

IEDEA-COHRE: Results based on 951,855 adults from 55 countries after imputation of missing data. Does not include "re-starters" after interruption.
Fig 2. Cumulative incidence (competing risks analysis) of disengagement, transfer (including silent transfers), and mortality, as estimated by a flexible parametric survival model based on time to disengagement from cohort entry date to 31 December 2014.
SMART study: RCT of stopping vs continuing ART if CD4 >350

CD4 change

NEJM 2006;355:2283
35% never on ART

40% failing or interrupted ART

Meintjes, Medicine 2015
GUIDELINES FOR
MANAGING ADVANCED
HIV DISEASE AND
Rapid Initiation
OF ANTIRETROVIRAL
THERAPY
JULY 2017
WHO definition of advanced HIV disease

For adults and adolescents, and children older than five years, advanced HIV disease is defined as CD4 cell count $<200\text{cells/mm}^3$ or WHO stage 3 or 4 event.

*Includes both ART naïve individuals and those who interrupt treatment and return to care*

All children younger than five years old with HIV are considered as having advanced HIV disease.
WHO Recommendation

A package of interventions including screening, treatment and/or prophylaxis for major opportunistic infections, rapid ART initiation* and intensified adherence support interventions should be offered to everyone presenting with advanced HIV disease.

* linked recommendation

Strong recommendation, moderate-quality evidence
WHO criteria for referral to hospital

- A seriously ill adult or adolescent is defined as having any of the following danger signs: respiratory rate $\geq 30$ breaths per minute; heart rate $\geq 120$ beats per minute; or unable to walk unaided. Other clinical conditions, such as body temperature $\geq 39^\circ C$ can also be considered based on local epidemiology and clinical judgement.

- A seriously ill child is defined as having any of the following danger signs: lethargy or unconsciousness; convulsions; unable to drink or breastfeed; and repeated vomiting. Other clinical conditions such as body temperature $\geq 39^\circ C$ and age-defined tachycardia and/or tachypnoea can be considered based on clinical judgement.

Not backed up by good evidence
SA – all pregnant PLWH
(studies showed high proportion culture+ & asymptomatic)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Intervention</th>
<th>CD4 cell count</th>
<th>Adults</th>
<th>Adolescents</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sputum Xpert® MTB/RIF as the first test for TB diagnosis among symptomatic people</td>
<td>Any</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>LF-LAM for TB diagnosis among people with symptoms and signs of TB</td>
<td>≤100 cells/mm³ or at any CD4 count if seriously ill</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Cryptococcal antigen screening</td>
<td>≤100 cells/mm³</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
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</tbody>
</table>
How to screen for TB
Development of a Standardized Screening Rule for Tuberculosis in People Living with HIV in Resource-Constrained Settings: Individual Participant Data Meta-analysis of Observational Studies

Haileyesus Getahun\textsuperscript{1}, Wanitchaya Kittikraisak\textsuperscript{2}, Charles M. Heilig\textsuperscript{3}, Elizabeth L. Corbett\textsuperscript{4}, Helen Ayles\textsuperscript{4,5}, Kevin P. Cain\textsuperscript{3}, Alison D. Grant\textsuperscript{4}, Gavin J. Churchyard\textsuperscript{6}, Michael Kimerling\textsuperscript{7}, Sarita Shah\textsuperscript{8}, Stephen D. Lawn\textsuperscript{4,9}, Robin Wood\textsuperscript{9}, Gary Maartens\textsuperscript{10}, Reuben Granich\textsuperscript{1}, Anand A. Date\textsuperscript{3}, Jay K. Varma\textsuperscript{2,3}
Best symptom screen for TB – any one of:
  • Cough – active (any duration)
  • Fever >2 weeks
  • Night sweats
  • Weight loss

Sensitivity improved:
  • Clinical vs community setting
  • **Not previously screened for TB**
  • Lower CD4 count
Effect of ART on WHO TB symptom screen: WHO meta-analysis

<table>
<thead>
<tr>
<th></th>
<th>On ART (n=4640)</th>
<th>Not on ART (n=8664)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sensitivity</strong></td>
<td>51.0% (28.4, 73.2)</td>
<td>89.4% (83.0, 93.5)</td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
<td>70.7% (47.8, 86.4)</td>
<td>28.1% (18.6, 40.1)</td>
</tr>
<tr>
<td><strong>Negative predictive value:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TB prevalence 1%</td>
<td>99.3%</td>
<td>98.0%</td>
</tr>
<tr>
<td>TB prevalence 5%</td>
<td>96.5%</td>
<td>96.0%</td>
</tr>
</tbody>
</table>

Lancet HIV 2018; 5: e515–23
Screen for cryptococcal antigen
Cryptococcal meningitis mortality: South Africa

- **Cape Town** (Bicanic, Clin Infect Dis 2007 & 2008)
  - 24 - 37% 10 week mortality

- **Gauteng** (Park, Int J STD AIDS 2011)
  - 41% survival at 90 days

- **Rural Kwazulu-Natal** (Lessells, SAMJ 2011)
  - 41% in-hospital mortality
  - 11% alive in ART care at 2 years
Cryptococcal antigenaemia precedes meningitis

In a Ugandan study antigenaemia preceded meningitis by median 22 days (>100 days in 11%)

French, AIDS 2002;16:1031
Prevalence of CrAg+ in adults CD4 <100:
Overall 6.48%
<table>
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<tbody>
<tr>
<td>Co-trimoxazole prophylaxis&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&lt;=350 cells/mm&lt;sup&gt;3&lt;/sup&gt; or clinical stage 3 or 4</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes; For criteria, see Annex 1</td>
</tr>
<tr>
<td>TB preventive treatment&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Any</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Fluconazole preemptive therapy for cryptococcal antigen–positive people without evidence of meningitis</td>
<td>&lt;100 cells/mm&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Yes</td>
<td>Yes</td>
<td>Not applicable (screening not advised)</td>
</tr>
</tbody>
</table>

<sup>a</sup> SA CD4 <200

Table 1 Components of the package of care for people with advanced HIV disease
TB preventive therapy
In settings with high TB incidence and transmission, adults and adolescents living with HIV who have an unknown or a positive TST and are unlikely to have active TB disease should receive at least 36 months of IPT, regardless of whether they are receiving ART. IPT should also be given irrespective of the degree of immunosuppression, history of previous TB treatment and pregnancy. (Conditional recommendation, low-quality evidence. Existing recommendation)
12H vs placebo with ART, Khayelitsha

Hazard ratio 0.63 (95% CI 0.41-0.94)

Number needed to treat (prevent 1 case TB) = 25
Number needed to harm (stop study drug due to toxicity) = 100

Rangaka Lancet 2014
Coming soon: rifapentine + INH

• Weekly RPT + INH for 12 doses as effective as 6-9 months INH, adverse events similar

• RPT induces metabolizing enzymes & drug transporters
  • Less marked than rifampicin when given weekly
  • DTG concentrations lowered – OK if VL suppressed (study to assess interaction in people starting DTG to start soon)

• Daily RPT + INH for 1 month as effective as 9 months INH
  • Drug-drug interactions will be worse

• RPT now registered in SA – FDC awaited

Pre-emptive therapy for CrAg+
Evidence for efficacy of prophylactic fluconazole in CrAg+

- No RCT vs placebo limited to CrAg+ patients
- Cochrane review identified 9 RCTS evaluating primary fluconazole or itraconazole prophylaxis for fungal infections
- Relative risk:
  - Cryptococcal disease: 0.29 (95% CI 0.17 to 0.49)
  - Cryptococcal mortality: 0.29 (95% CI 0.11 to 0.72)
REMSTART trial

• Open-label, randomised controlled trial
• 6 urban clinics in Tanzania and Zambia
• Age ≥18 years
• CD4 count <200 cells per μL
• ART naïve
• Randomly assigned to standard care versus standard care plus:
  • CrAg screening & fluconazole 800 mg/d for 2 wk, then 400 mg/d for 8 weeks if CrAg+
  • Weekly home visits for the first 4 weeks on ART by lay workers to provide support
• Primary endpoint: Mortality at 12 months
28% reduction in mortality

Mfinanga, Lancet 2015
Perform serum CrAg test when CD4 <100 cells/mm³

Positive

Negative

Lumbar puncture (LP)

CSF +ve for CrAg

Induction phase:
Amphotericin B, IV, 1.0 mg/kg/day for 14 days AND
Fluconazole, oral, 1200 mg daily for 14 days

Consolidation phase:
Fluconazole, oral, 800 mg daily for 2 months AND
Start ART after 4 weeks of antifungal therapy

Maintenance phase:
Fluconazole, oral, 200 mg daily
Continue fluconazole for at least 1 year in total, and discontinue when CD4 > 200 cells/mm³ on ART and virological suppressed

CSF -ve for CrAg

Induction phase:
Fluconazole, oral 1200 mg daily for 2 weeks

Consolidation phase:
Fluconazole, oral, 800 mg daily for 2 months AND
Start ART after 2 weeks of antifungal therapy

Start ART
Screen for other OIs
<table>
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<tr>
<td>Rapid ART initiation (as recommended in Chapter 3)</td>
<td>Any</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Defer initiation if clinical symptoms suggest TB or cryptococcal meningitis (see Chapter 3)</td>
<td>Any</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Tailored counselling to ensure optimal adherence to the advanced disease package, including home visits if feasible</td>
<td>&lt;200 cells/mm³</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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</table>
When to start ART after cryptococcal meningitis

RCT in ART naïve in SA & Uganda: start ART early (median 9 days) vs deferred (median 36 days)

NEJM 2014;370:2487
When to start ART after TB

Meta-analysis of 8 RCTs evaluating early (1-4 weeks) vs deferred (8-12 weeks) ART in patients with TB

Mortality: CD4 <50 early ART (RR 0.71 [CI, 0.54 to 0.93])
            CD4 >50 early ART (RR 1.05 [CI, 0.68 to 1.61])

TB-IRIS: Early ART ↑ risk (RR, 2.31 [CI, 1.87 to 2.86])

SA guidelines: CD4 <50 start ART at 2 weeks
                 CD4 >50 start ART at 8 weeks