National consolidated guidelines for the prevention of mother-to-child transmission of HIV (PMTCT) and the management of HIV in children, adolescents and adults

24 December 2014

1. Key principles

In the context of antiretroviral therapy (ART),

- ART guidelines are evolving. Internationally, the current guidelines have been written in addition to those relevant to Southern Africa. The following general principles underpin the ART process:

- South Africa has a multi-sectoral approach to HIV care and treatment. Children are a priority in the region;

- Treatment and diagnostic services are available through various African health systems.

- National and provincial guidelines are in place to ensure that treatment and diagnostic services are provided to all those in need.

- This includes the need for ART guidelines in order to provide effective care and treatment for children and adolescents.

- There is a need for ART guidelines to be based on the best available evidence.

- ART guidelines are developed through a process of evidence-based decision-making.

- Guidelines provide a framework for the implementation of ART in a given context.

- Guidelines should be updated regularly to reflect new evidence and changing clinical practices.

- Guidelines should be accessible and understandable to health-care providers.

- guidelines should be translated into practice through regular monitoring and evaluation.

2. Goals of ART

The primary goals of ART are:

- improvement in health outcomes;

- reduction in HIV incidence and mortality;

- reduction in maternal mortality and morbidity;

- reduction in the transmission of HIV to infants;

- reduction in the transmission of HIV to adults;

- reduction in the transmission of HIV to children;

- reduction in the transmission of HIV to adolescents;

- reduction in the transmission of HIV to adults and children.

3. Standard of care

The standard of care for ART includes:

- ensuring that ART is provided to all those in need;

- providing ART in a timely manner;

- ensuring that ART is provided in a culturally appropriate manner;

- ensuring that ART is provided in a respectful manner;

- ensuring that ART is provided in a confidential manner.

4. Access to ART

Access to ART is crucial for the implementation of effective ART programs. This includes:

- ensuring that ART is provided to all those in need;

- ensuring that ART is provided in a timely manner;

- ensuring that ART is provided in a culturally appropriate manner;

- ensuring that ART is provided in a respectful manner;

- ensuring that ART is provided in a confidential manner.

5. Monitoring and evaluation

Monitoring and evaluation are essential for the implementation and success of ART programs. This includes:

- ensuring that ART is provided to all those in need;

- ensuring that ART is provided in a timely manner;

- ensuring that ART is provided in a culturally appropriate manner;

- ensuring that ART is provided in a respectful manner;

- ensuring that ART is provided in a confidential manner.

6. Conclusion

The implementation of effective ART programs is essential for the prevention of mother-to-child transmission of HIV and the management of HIV in children, adolescents and adults. This includes:

- ensuring that ART is provided to all those in need;

- ensuring that ART is provided in a timely manner;

- ensuring that ART is provided in a culturally appropriate manner;

- ensuring that ART is provided in a respectful manner;

- ensuring that ART is provided in a confidential manner.
Topics

1. What CD4 threshold to start ART at?
2. Return to care after 1\textsuperscript{st} line interruption
3. Patients with viraemia on 2\textsuperscript{nd} line
4. Cryptococcal antigen screening
Topics

1. What CD4 threshold to start ART at?
2. Return to care after 1\textsuperscript{st} line interruption
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4. Cryptococcal antigen screening
Case scenario

• 28 yr man
• Newly diagnosed with HIV in HCT service
• CD4 count = 478
• Asymptomatic
• He asks you:
  “Why do I need to start ART now?”
Evolution of NDOH guidelines

What evidence drove this?

2004 CD4<200

2010 CD4<350 for some

2013 CD4<350 for all

2015 CD4<500
Haiti trial
Starting ART at CD4<350 vs CD4<200 or AIDS

HR = 4.0

HR = 2.0

Severe, NEJM 2010
HPTN 052 trial

Botswana, Brazil, India, Kenya, Malawi, SA, Thailand, Zimbabwe, USA

1736 serodiscordant, sexually active couples with HIV+ partner having CD4 350-550 randomised 1:1 to:

– Immediate ART
– Delay ART until CD4 ≤ 250 or Stage 4 event

Cohen, NEJM 2011;365:493
Early ART reduced HIV transmission

HR = 0.11
95% CI = 0.04-0.32

HR = 0.04
95% CI = 0.01-0.27

89% down

96% down

Cohen, NEJM 2011;365:493
ART scale-up associated with lower HIV incidence in rural KZN

- 16,667 HIV-negative adults followed 2004-11
- Annual HIV prevalence and ART coverage in a 3km radius around each individual was calculated
- Hazard ratio for HIV seroconversion in relation to ART coverage calculated
  - Adjusted for gender, age, HIV prevalence and various HIV risk behaviours
- 1,413 seroconversions observed over 53,605 years of observation
  - Crude HIV incidence = 2.6/100 person-years

Tanser, Science 2013;339:966
Researchers linked: HIV surveillance database ART clinics database

ART coverage 2005 - 2011

HIV prevalence 2005 - 2011

Tanser, Science 2013;339:966
Increased ART coverage associated with reduced HIV incidence (dose-response relationship)

Tanser, Science 2013;339:966
START Study
Strategic Timing of AntiRetroviral Treatment Study

- Adult ART naïve patients with CD4 > 500
- Randomised to:
  - Immediate ART
  - Start when CD4 < 350
- 215 sites in 35 countries
- 4,685 patients enrolled
- Due to end late 2016
- Stopped early by DSMB and results announced on 27 May 2015 (average 3 years follow-up)
FOR IMMEDIATE RELEASE
Wednesday, May 27, 2015

National Institute of Allergy and Infectious Diseases (NIAID)
http://www.niaid.nih.gov

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NIAID Office of Communications
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Starting Antiretroviral Treatment Early Improves Outcomes for HIV-Infected Individuals

NIH-Funded Trial Results Likely Will Impact Global Treatment Guidelines

A major international randomized clinical trial has found that HIV-infected individuals have a considerably lower risk of developing AIDS or other serious illnesses if they start taking antiretroviral drugs sooner, when their CD4+ T-cell count—a key measure of immune system health—is higher, instead of waiting until the CD4+ cell count drops to lower levels. Together with data from previous studies showing that antiretroviral treatment reduced the risk of HIV transmission to uninfected sexual partners, these findings support offering treatment to everyone with HIV.

The new finding is from the Strategic Timing of AntiRetroviral Treatment (START) study, the first large-scale randomized clinical trial to establish that earlier antiretroviral treatment benefits all HIV-infected individuals. The National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health, provided primary funding for the START trial. Though the study was expected to conclude at the end of 2016, an interim review of the study data by an independent data and safety monitoring board (DSMB) recommended that results be released early.
Event rate of primary endpoint

- Primary endpoint = AIDS, serious non-AIDS event* or death

- Early arm = 0.60/100 person years
- Deferred arm = 1.25/100 person years

- Hazard ratio = 0.47 (95% CI = 0.32-0.68)  
  (53% reduction in early arm)

* Serious non-AIDS event = Major CVS, renal or hepatic disease or non-AIDS cancer
<table>
<thead>
<tr>
<th>Category 1: AIDS, serious non-AIDS, or death (primary)</th>
<th>Early arm (A)</th>
<th>Later arm (B)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>41</td>
<td>86</td>
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<tr>
<td>Category 2: AIDS or AIDS death.</td>
<td>14</td>
<td>46</td>
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<tr>
<td>Category 3: Serious non-AIDS or non-AIDS death.</td>
<td>28</td>
<td>41</td>
</tr>
</tbody>
</table>
Early ART & IPT in HIV-Infected African Adults With High CD4 Count (Temprano Trial)

- Randomized 2x2 factorial superiority trial conducted in 9 HIV care centers in Côte d’Ivoire
  - Immediate ART vs WHO criteria
  - 6 months IPT vs no IPT
- March 2008 - January 2015
- Inclusion criteria were:
  - HIV-1 infection
  - Age >18 years
  - CD4 nadir <800/ul
  - No criteria for starting ART according to the most recent WHO guidelines
- 2076 randomised; 2056 included in analysis
  (median CD4 = 465)

Danel, CROI 2015, 115LB
The primary endpoint was severe HIV morbidity (AIDS-defining diseases, non-AIDS-defining malignancy, or non-AIDS-defining invasive bacterial diseases), or any-cause mortality at 30 months.

<table>
<thead>
<tr>
<th>Severe morbidity</th>
<th>N</th>
<th>TAR (PY)</th>
<th>Rate (/100PY)</th>
<th>AHR</th>
<th>(95% CI)</th>
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<tr>
<td>Overall</td>
<td></td>
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<td>2,310</td>
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<td>(0.41 - 0.76)</td>
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<td>IPT</td>
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<td>Baseline CD4 &gt;500/ul</td>
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<td>38</td>
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<td>964</td>
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<td>IPT</td>
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<td>(0.37 - 1.02)</td>
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</tbody>
</table>

N: number of events. PY: person-years; TAR: time at risk; AHR: adjusted hazard ratio; CI: confidence interval
“We now have clear-cut proof that it is of significantly greater health benefit to an HIV-infected person to start antiretroviral therapy sooner rather than later.”

“Moreover, early therapy conveys a double benefit, not only improving the health of individuals but at the same time, by lowering their viral load, reducing the risk they will transmit HIV to others. These findings have global implications for the treatment of HIV.”
Guidelines are likely to change

CD4 < 500

All HIV+ patients regardless of CD4

Prioritise those with lowest CD4 counts
Patients must be motivated for lifelong ART
Topics

1. What CD4 threshold to start ART at?
2. Return to care after 1\textsuperscript{st} line interruption
3. Patients with viraemia on 2\textsuperscript{nd} line
4. Cryptococcal antigen screening
Case scenario

- Baseline CD4 = 180
- Viral load suppressed on 1st line for 18 months
- Family crisis, stops ART and only returns to care 11 months later
- No TB symptoms and generally well
- What do you do?
SA HIV CLINICIANS SOCIETY (1)

• We recommend restarting the same regimen if patients return to care after defaulting therapy.
• A VL should preferably be performed before restarting. We then recommend that the VL is measured 3 months after restarting ART; switching to a second-line regimen should be considered if the VL is not <1 000 copies/mL at this point.
• In patients with multiple episodes of interruption, particularly beyond the first year of ART, many clinicians would consider switching to a second-line regimen, making the assumption that the multiple interruptions resulted in first-line resistance.
• Reasons for defaulting should be addressed and adherence support increased.

SA HIV Clin Soc guidelines, 2014
Hospitalisation with an AIDS-defining condition and a CD4+ count of <50 cells/μL represents another situation where a patient may be restarted immediately on second-line ART when returning to care after defaulting. The reason being that the patient is considered to be at high risk of mortality if restarted on a first-line therapy to which their virus may be resistant, and that they require a guaranteed effective ART regimen immediately.

This decision should usually be taken by the clinicians at a hospital level.

SA HIV Clin Soc guidelines, 2014
If the patient **has interrupted treatment** and was on a previous regimen as above, or where the prior regimen is unknown, take a full history to establish why the treatment was stopped. If the interruption was NOT due to toxicity or clear virological failure, check the VL and restart first line treatment as above, and **repeat the VL after 2 months**.

If patients **have failed a previous regimen**, initiate appropriate second line treatment.

If patient was **previously on ART but has interrupted treatment**, establish the cause of the interruption. If it is due to social or psychological factors, address these and follow up on interventions. If the patient stopped as a result of side effects, evaluate other drug choices and offer appropriate options. If the interruption was due to drug supply issues, and there were no non-adherence, resistance or toxicity issues, the previous ART regimen should be reinitiated as soon as possible.

SA NDOH guidelines
General points

• Issues to consider
  – History of adherence prior to default episode
  – Viral load measures prior to default episode
  – CD4 nadir and current CD4
  – Current clinical status

• In most cases restart 1st line
  – Do not want to unnecessarily switch to 2\textsuperscript{nd} line (less well tolerated)

• Some exceptions
  – Not wanting to restart patient on failing regimen if very immunosuppressed and/or very unlikely to be effective

• If restart first line (especially in patients with CD4 < 200)
  – Do viral load when restart then at 2-3 months, anticipate > 2 log drop if adherent and no resistance
  – Most will have VL < 1000 by 3 months
Virological Failure and Drug Resistance in Patients on Antiretroviral Therapy After Treatment Interruption in Lilongwe, Malawi

Julia Luebbert,1,2 Hannock Tweya,3,5 Sam Phiri,3 Thom Chaweza,3 Johnbosco Mwafilase,3 Mina C. Hosseinipour,4 Heribert Ramroth,1 Paul Schnitzler,2 and Florian Neuhann1

133 patients
Mean duration of ART prior to interruption 14 months
After a minimum of 2 months following ART resumption:
  ● VL was undetectable in 81 (60.9%)
  ● 400–1000 copies/mL in 12 (9.0%)
  ● ≥1000 copies/mL in 40 (30.1%)
Drug-resistance testing successful for 36 of 40 patients
  ● NNRTI mutations in 32 of 133 (24.1%)
  ● NNRTI + NRTI mutations in 27 of 133 (20.3%)

Clin Infect Dis 2012
Topics

1. What CD4 threshold to start ART at?
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4. Cryptococcal antigen screening
Case scenario

- Patient on 2\textsuperscript{nd} line for 3 years has viral load of 450,000 copies/ml after being undetectable

- When would you do genotype resistance test?
HIV RNA >1000 copies/ml on second-line ART for longer than one year

Check for adherence, compliance, tolerability and drug-drug interaction and assess psychological issues

Repeat VL after 6 months

VL ≤1000 copies/ml
- Continue second-line regimen

VL >1000 copies/ml
- Specialist referral as needed

Genotypic resistance testing
- Specialist decision regarding further management
Consideration for Genotype & 3rd line

- Repeated VL > 1000 on 2nd line ART
- On 2nd line > 1 year
- Of those with virological failure on 2nd line majority do not have resistance*
- Critical to ensure adherence
  - Pharmacy claims records for the last 6 months is objective method (specific but not sensitive)
- Adherence counseling and address side effects
- Ask re previous exposure to rifampicin without lopinavir/ritonavir dose adjustment

HIVdb Program: Mutation List Analysis

Protease, RT, and integrase mutations can be entered using either the text box or pull down menus (detailed usage is found below).

The output can then be customized to display mutation comments, mutation scores, and an optional identifier and date. For further explanations and sample datasets please see the Release Notes.

Reverse Transcriptase

Enter Mutation List:

OR

Use The Pulldown Menus:

Protease

http://hivdb.stanford.edu/
### Mutation Scoring

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<th>PR</th>
<th>ATV/r</th>
<th>DRV/r</th>
<th>FPV/r</th>
<th>IDV/r</th>
<th>LPV/r</th>
<th>NFV</th>
<th>SQV/r</th>
<th>TPV/r</th>
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### RT 3TC ABC AZT D4T DDI FTC TDF EFV ETR NVP RPV

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MUTATION SCORING

Mutation scoring

The mutation penalty score for an antiretroviral drug is obtained by adding together the scores of each mutation associated with resistance to that drug. The scores are titrated to fall within the following ranges:

- **0-9:** Drug susceptible
- **10-14:** Potential low level resistance
- **15-29:** Low level resistance
- **30-59:** Intermediate resistance
- **>60:** High level resistance
### Drug Resistance Interpretation: RT

<table>
<thead>
<tr>
<th>NRTI Resistance Mutations:</th>
<th>M41L, K70R, Q151M</th>
</tr>
</thead>
<tbody>
<tr>
<td>NNRTI Resistance Mutations:</td>
<td>None</td>
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<tr>
<td>Other Mutations:</td>
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<table>
<thead>
<tr>
<th>Nucleoside RTI</th>
<th>Non-Nucleoside RTI</th>
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</thead>
<tbody>
<tr>
<td>lamivudine (3TC)</td>
<td>delavirdine (DLV)</td>
</tr>
<tr>
<td>abacavir (ABC)</td>
<td>efavirenz (EFV)</td>
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<td>zidovudine (AZT)</td>
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<td>stavudine (D4T)</td>
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<td>tenofovir (TDF)</td>
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<tr>
<td>Intermediate resistance</td>
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### RT Comments

- **NRTI**
  - M41L usually occurs with T215Y. Together these mutations confer intermediate-to-high level resistance to AZT and d4T and a lower level of resistance to ddl, ABC, and TDF.
  - K70R causes low-level AZT, d4T, and possibly TDF resistance.
  - By itself, Q151M causes intermediate-to-high level resistance to AZT, ddl, d4T, and ABC; and low-level resistance to TDF. With changes at the associated positions 75, 77, and 116, Q151M confers high-level resistance to AZT, ddl, d4T, and ABC; intermediate resistance to TDF, and low-level resistance to 3TC and FTC.
Third line options

• **NRTIs with best resistance profile**

• New generation NNRTIs
  – Etravirine (and rilpivirine)
  – NNRTI genotype unreliable at 2\textsuperscript{nd} line failure

• **Ritonavir-boosted darunavir**

• **Raltegravir**

• **Maraviroc** *(cost+++ , only if purely CCR5 tropic)*

• **Dolutegravir** *(to be registered later this year)*
## CASE 1: GT while failing 2\textsuperscript{nd} line

<table>
<thead>
<tr>
<th>Class</th>
<th>Mutations</th>
</tr>
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<tbody>
<tr>
<td>NRTIs</td>
<td>M184V</td>
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<tr>
<td>NNRTIs</td>
<td>K103N</td>
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<td>PIs</td>
<td>Mo major mutations</td>
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</table>

- Explanation?
- Management?
CASE 2: GT while failing 2nd line

<table>
<thead>
<tr>
<th>Class</th>
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<tr>
<td>NRTI</td>
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<tr>
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<td>A98G, F227L</td>
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<tr>
<td>PI</td>
<td><strong>M46I, I54V, L76V, V82A</strong>, L10IV, Q85E, A71I</td>
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# Mutation Scoring

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<thead>
<tr>
<th>PR</th>
<th>ATV/r</th>
<th>DRV/r</th>
<th>FPV/r</th>
<th>IDV/r</th>
<th>LPV/r</th>
<th>NFV</th>
<th>SQV/r</th>
<th>TPV/r</th>
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<th>AZT</th>
<th>D4T</th>
<th>DDI</th>
<th>FTC</th>
<th>TDF</th>
<th>EFV</th>
<th>ETR</th>
<th>NVP</th>
<th>RPV</th>
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<tbody>
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<td>20</td>
<td>25</td>
<td>10</td>
<td>60</td>
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</tr>
</tbody>
</table>
Management

• 3rd line:
  – TDF/FTC + Raltegravir + Darunavir/ritonavir

• Follow-up viral loads:
  – Less than 40 for over 2 years
Topics

1. What CD4 threshold to start ART at?
2. Return to care after 1st line interruption
3. Patients with viraemia on 2nd line

4. Cryptococcal antigen screening
<table>
<thead>
<tr>
<th>Phase of HIV management</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HIV diagnosis</strong></td>
<td></td>
</tr>
<tr>
<td>Confirm HIV result with rapid antibody test if no test results are available</td>
<td>To confirm HIV-positive status in patients who present without documented proof of positive HIV status</td>
</tr>
<tr>
<td>WHO clinical staging if HIV-positive</td>
<td>To assess eligibility for ART and timing of initiation</td>
</tr>
<tr>
<td>CD4 count</td>
<td>To identify eligibility for ART (CD4 &lt;500/μl)</td>
</tr>
<tr>
<td></td>
<td>To identify eligibility for prioritisation (CD4 &lt;350/μl)</td>
</tr>
<tr>
<td></td>
<td>To identify eligibility for fast-tracking (CD4 &lt;200/μl)</td>
</tr>
<tr>
<td></td>
<td>To identify eligibility for Cotrimoxazole (CD4 &lt;200/μl)</td>
</tr>
<tr>
<td></td>
<td>To identify eligibility for CrAg or CLAT (CD4 &lt;100/μl)</td>
</tr>
<tr>
<td>Screen for pregnancy or ask if planning to conceive</td>
<td>To identify women who need ART for PMTCT and offer appropriate family planning</td>
</tr>
<tr>
<td>Assessment of hypertension and diabetes with blood pressure and urine glycosuria</td>
<td>To identify any concomitant chronic diseases</td>
</tr>
<tr>
<td>Screen for TB symptoms using the TB screening tool</td>
<td>To identify those suspected of TB and refer them for investigation and to assess eligibility for INH</td>
</tr>
<tr>
<td>Screen for HBV (HBsAg)</td>
<td>To identify those co-infected with HBV so that they can be initiated on ART regardless of CD4 count</td>
</tr>
<tr>
<td>Screening for STIs and syphilis</td>
<td>To identify and treat STIs</td>
</tr>
<tr>
<td>Weight and height in adolescent</td>
<td>To check if the weight is above or below 40kg to determine which ARV drugs to use</td>
</tr>
<tr>
<td><strong>Cryptococcus Antigen (CrAg) test if CD4 &lt;100 cells/μl</strong></td>
<td>To assess if there is disseminated Cryptococcal infection and if fluconazole treatment/prophylaxis is indicated</td>
</tr>
<tr>
<td>Do Hb or FBC if requires AZT</td>
<td>To detect anaemia or neutropenia</td>
</tr>
<tr>
<td>Creatinine if requires TDF</td>
<td>To assess renal sufficiency</td>
</tr>
<tr>
<td>ALT if requires NVP</td>
<td>To exclude liver dysfunction</td>
</tr>
<tr>
<td>Fasting cholesterol and triglycerides if requires LPV/r</td>
<td>To identify at risk of LPV/r related hyperlipidaemia. If above 6 mml/L, consider (ATV/r) instead of LPV/r (if available)</td>
</tr>
</tbody>
</table>
Case scenario

• ART naïve patient with CD4 = 55

• Attends ART clinic and tested for serum cryptococcal antigen = POSITIVE

• What do you do?
In a Ugandan study: Antigenaemia preceded meningitis by median 22 days (>100 days in 11%)

French, AIDS 2002;16:1031
Retrospective testing of plasma of 707 patients who started ART 2002-2005

- 336 with CD4 ≤ 100
- 42 CrAg + (13%)
- 21 no history of CM
- 6 (29%) developed CM on ART
- 4 (19%) others died or lost to follow-up

Among those who were CrAg negative none developed CM
% of patients without prior CM who were CrAg +

Jarvis et al, Clin Infect Dis 2009;48:856
CrAg Lateral Flow Assay

1. Add 1 drop LF specimen diluent to tube.
2. Add 40 µL patient specimen to tube.
3. Insert strip as shown.
4. Wait 10 minutes.
5. Positive/Negative results.

Source: Immy CrAg LFA package insert
Cryptococcal antigen screening when CD4+ T-lymphocyte count <100 cells/µl

- Contact patient for urgent follow-up
- Screen for symptoms of meningitis
- Check for special situations

| Symptomatic | Asymptomatic
|-------------|-------------|
| Start fluconazole 1200 mg daily and refer immediately for lumbar puncture | Lumbar puncture (+) or Lumbar puncture (-)

Lumbar puncture (+) pathway:
- Amphotericin B plus fluconazole:
  - 800 mg daily for 2 weeks in hospital

Lumbar puncture (-) pathway:
- Start ART after 2 weeks of antifungal therapy

Fluconazole 400 mg daily for 2 months then 200 mg daily
Continue fluconazole for minimum of 1 year in total and discontinue when patient has had two CD4 counts >200 taken at least 6 months apart

Start ART after 4-6 weeks of antifungal therapy
Start ART after 2 weeks of antifungal therapy

No clinical trials data regarding pre-emptive treatment

SA HIV Clinicians Society 2013
Cryptococcal meningitis screening and community-based early adherence support in people with advanced HIV infection starting antiretroviral therapy in Tanzania and Zambia: an open-label, randomised controlled trial

Sayoki Mfinanga, Duncan Chanda, Sokoine L Kivuyo, Lorna Guinness, Christian Bottomley, Victoria Simms, Carol Chijoka, Ayubu Masasi, Godfather Kimaro, Bernard Ngowi, Amos Kahwa, Peter Mwaba, Thomas S Harrison, Saidi Egwaga, Shabbar Jaffar, on behalf of the REMSTART trial team*
28% reduction in mortality

Number at risk

<table>
<thead>
<tr>
<th></th>
<th>Clinic plus community support</th>
<th>Standard care</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
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<td>998</td>
</tr>
<tr>
<td>3</td>
<td>899</td>
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<td>9</td>
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<td>811</td>
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<tr>
<td>12</td>
<td>842</td>
<td>794</td>
</tr>
</tbody>
</table>
Take home messages

1. Now evidence of individual clinical benefit from initiating ART even at CD4 counts > 500.
2. If patient defaults 1\textsuperscript{st} line and returns, generally restart 1\textsuperscript{st} line and monitor VL closely. There are exceptions.
3. First evaluate adherence objectively before considering genotype and 3\textsuperscript{rd} line in patients failing 2\textsuperscript{nd} line.
4. Cryptococcal antigen screening and pre-emptive fluconazole reduces mortality at a programmatic level.
Steve Andrews

Friend, colleague, teacher and stalwart of the Clinicians Society