Increasing HIV treatment for TB patients – thinking out of the box

Anthony D Harries, The Union

Paris, France
## Achievements against Global Plan Targets

<table>
<thead>
<tr>
<th>Activity</th>
<th>Country Reports 2007</th>
<th>Global Plan Target 2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of TB patients tested for HIV</td>
<td>900,000</td>
<td>2,000,000</td>
</tr>
<tr>
<td>Number of HIV-positive TB patients started on CPT</td>
<td>200,000</td>
<td>600,000</td>
</tr>
<tr>
<td>Number of HIV-positive TB patients started on ART</td>
<td>100,000</td>
<td>300,000</td>
</tr>
</tbody>
</table>

*WHO Report 2009 Global Tuberculosis Control*
ART provision in estimated number of HIV-TB patients

<table>
<thead>
<tr>
<th>Estimated number of HIV-positive TB patients in 2007</th>
<th>1,370,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of diagnosed HIV-positive TB patients enrolled to ART in 2007</td>
<td>100,000 (7.3%)</td>
</tr>
</tbody>
</table>

*WHO Report 2009 Global Tuberculosis Control*
Step 1: increase reliable HIV testing in TB patients
Ensure all TB registration centres have easy access to HIV testing and advocate for quality assurance.
Why are some patients with TB not HIV tested in Malawi

- Irregular supply of HIV test kits
- HIV counsellors “temporarily” out
- Staff forget to refer patients for testing
- Patients decide to go home, decline, etc
- Patients already HIV tested, and no one asks
A BETTER APPROACH

Patient diagnosed with TB

Registration with TB officer: completion of TB treatment card

HIV testing and counselling

Enter results to treatment card, return to TB officer and complete registration: enter results to TB Register

Start anti-TB treatment
Remember to ask about previous HIV test

• If previous test was POSITIVE, then record patient as HIV-positive and no need to do more

• If previous test was NEGATIVE, if done 3 months or longer previously then the test should be repeated
Step 2: Match TB treatment centres with ART clinics
Many TB clinics are decentralised, therefore....

• Decentralise ART clinics
• Task shifting to manage ART
• Simple standardised models of care
• Limited laboratory monitoring

**TWO MAIN QUESTIONS:-**

• Services within the same clinic?
• How far to reach out into the community?
Probability of attrition (deaths, loss to follow up and stopped) at district hospital and health centres, Thyolo, Malawi

[Massaquoi et al, TRSTMH 2009]
Step 3: Place all HIV-TB patients on ART
<table>
<thead>
<tr>
<th>CD4 Cell Count</th>
<th>ART Recommendations</th>
<th>Timing of ART in relation to start of TB treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4 &lt; 200 cells/mm³</td>
<td>Recommend ART a</td>
<td>Between 2 and 8 weeks (in initial phase of TB treatment) b</td>
</tr>
<tr>
<td>CD4 between 200 and 350 cells/mm³</td>
<td>Recommend ART</td>
<td>After 8 weeks (in continuation phase of TB treatment)</td>
</tr>
<tr>
<td>CD4 &gt; 350 cells/mm³</td>
<td>Defer ART c</td>
<td>Re-evaluate the patient at 8 weeks and at the end of TB treatment</td>
</tr>
<tr>
<td>Not available</td>
<td>Recommend ART d</td>
<td>Between 2 and 8 weeks</td>
</tr>
</tbody>
</table>

a An efavirenz (EFV)-containing regimen is the preferred first-line regimen
b ART should start as soon as TB treatment is tolerated, esp in patients with severe immunosuppression
c ART should be started if other non-TB stage 3 or stage 4 events are present
d For some TB diagnoses that generally respond well to anti-TB therapy (e.g., lymph node TB, uncomplicated pleural effusion), deferral of ART should be considered.
Thus….

Between 10-20% of HIV-TB patients currently do not start ART because their CD4 count is too high.
In 2007.....

• All HIV-positive TB patients in Malawi potentially eligible for ART [Stage 3 or 4]

• There were an estimated 17,800 HIV-positive TB patients

• 4,573 (26%) HIV positive TB patients started ART
Step 4: Start ART early in TB treatment (in first month)
Current debate about when to start ART

**Early (first 1 month)**
- May reduce early deaths
- May improve sputum smear conversion
- May be advantage in drug-resistant TB

**But**
- Rif-NNRTI interaction
- High pill burden
- More additive toxicities
- IRIS in sick patient

**Later (after 2 months)**
- Easier to use ART in continuation phase TB Rx
- Pill burden less
- Patient more stable

**But**
- Less impact on TB deaths
  Uptake may be low as patients feel better
Problem with delayed ART

- Many HIV-TB deaths occur in the first two months of anti-TB treatment
- Thus, potential benefit of reducing mortality may be diminished
ART given during the Continuation Phase of TB treatment

- Observational study in Thyolo, Malawi
- 658 HIV+ve TB patients started TB therapy
- 576 completed 2 months IP (82 died)
- 180 started ART and 396 did not
- Incidence rates for death no different

[ Zachariah et al, IJTLDD 2007]
Survival of HIV+ve TB patients during the continuation phase (months 2 – 8) of anti-TB treatment in Thyolo

Survival probability in relation to ART

Log-rank test $X^2 = 0.34, P=0.6$

Zachariah et al, IJTLID 2007
Why not start ART at the same time as TB treatment!
Step 5: Use NVP with Rifampicin
Pharmacokinetic interactions: NNRTI / PI and rifampicin

- NNRTIs and PIs are metabolised through CYP450 enzymes in the liver

- Rifamycins are potent inducers of CYP450: rifampicin > rifapentine > rifabutin

- Rifampicin reduces:
  - NVP levels by 30-40%
  - EFV levels by 20-25%
  - PI levels by 70%
NVP and Rifampicin: jury still out..

<table>
<thead>
<tr>
<th>Evidence to support NVP</th>
<th>Evidence against NVP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virological outcomes similar in NVP versus EFV regimens in Botswana</td>
<td>Virological outcomes worse in NVP versus EFV regimens in South Africa</td>
</tr>
<tr>
<td>[Shipton et al, IJTLID 2009; 13: 360-6]</td>
<td>[Boulle et al, JAMA, 2008, 300; 530-9]</td>
</tr>
</tbody>
</table>
What we specifically need to know is….

- To what degree are NVP levels suppressed while on anti-TB treatment

- Does this suppression lead to increased rates of drug resistance and to increased rates of ART failure
Practical point - no need for starter phase of NVP

- Because of low NVP levels in patients on Rifampicin, there is no need to start with NVP 200mg OD

- Therefore if patient is on Rifampicin, start with NVP 200mg twice a day

Van Oosterhout et al, Antiviral Ther 2007; 12: 515-21
Other options….. not that relevant at the moment to increasing ART uptake

• Triple nucleoside ART

• Rifabutin

• Second line ART (so few patients on this)

• MDR- and XDR-TB
Step 6: Monitor and report on HIV parameters
**NATIONAL TUBERCULOSIS PROGRAMME MALAWI**

**TUBERCULOSIS TREATMENT CARD**

**Name:**

**Address:**

(in full)

**Name and address of Guardian:**

**Sex:**

M | F | Age: __________

**Disease**

P = Pulmonary TB  EP = Extra-pulmonary TB

**Class & Patient Category**

New = New case  Relap = Relapse  RAD = Retreatment after default  Fail = Treatment failure  Oth = Other previously treated

**Specify other:**

**Management of HIV+ Patients**

**ARV**

**CPT**

**Start Date:**

**ARV No.:**

**ARV-Status:**

A: started ARV before starting TB treatment
B: started ARV while on TB treatment
C: ARV not started by the time when discharged from TB treatment

**Update ARV-Status in Register from this card:**

**Documented HIV Test History (see back)**

**Update HIV-Status in Register from latest entry on card:**

RN or NN: HIV-Status Negative

PP or NP: HIV-Status Positive

NT or Unk: HIV-Status Unknown

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**1. INITIAL INTENSIVE PHASE**

**Regimen and daily dosage of tablets / grams of S**

<table>
<thead>
<tr>
<th>Regimen 1</th>
<th>Regimen 2</th>
<th>TB Meningitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>RHZE</td>
<td>RHZE</td>
<td>RHZ</td>
</tr>
<tr>
<td>R: rifampicin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H: isoniazid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Z: pyrazinamide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E: ethambutol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S: streptomycin (S for 2 months only in Regimen 2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Sputum Results**

<table>
<thead>
<tr>
<th>Time</th>
<th>Test</th>
<th>Date</th>
<th>Serial No</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initiation</td>
<td>smear culture</td>
<td></td>
<td></td>
<td>growth sensitivity</td>
</tr>
<tr>
<td>Month 2</td>
<td>smear</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Month 3*</td>
<td>smear</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Month 5</td>
<td>smear</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Last month 6th</td>
<td>smear</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Weight (kg):**

- Recent Negative
- Past Positive
- Never tested / old negative
- New HIV Test
- New Neg.
- New Pos.
- Not Tested

**DOT Option:**

Guardian | Hospital | Health Centre

**Month**

| Day * | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 |

**At 2 months:**

If HIV Positive, Start ART

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Version 3 March 2008
2. CONTINUATION PHASE (see guidelines)
Enter Prescribed regimen and dosages
(indicate number of tablets per dose)

<table>
<thead>
<tr>
<th>Regimen 1</th>
<th>Regimen 2</th>
<th>TB Meningitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ ] RH daily for 4 months</td>
<td>[ ] RHE daily for 5 months</td>
<td>[ ] RH daily for 7 months</td>
</tr>
</tbody>
</table>

**Documented HIV Test History**

- **Recent Negative:** Documented negative test within past 3 months → No new test needed this time
- **Past Positive:** Documented positive test from any time in the past
- **Never tested or old negative:** Previous test without documentation → All of these patients need a new HIV test
- **Unknown:** Current HIV-status unknown, HIV-testing was not discussed

| Month | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 |
|-------|---|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|

* Enter X on day of supervised drug administration or when drugs are collected (month EH collection for self administration). Whenever drugs are collected for self-supervised administration draw a horizontal line ( ———— ) to indicate number of days supply given.

Remarks: __________________________________________________________

______________________________________________________________
## Tuberculosis Register

<table>
<thead>
<tr>
<th>Registration Date</th>
<th>District TB Number</th>
<th>Name (in full)</th>
<th>Sex</th>
<th>Age</th>
<th>Age group</th>
<th>Place of Residence (in full)</th>
<th>Name of Treatment Unit</th>
<th>DOT Option (1)</th>
<th>Duration Current Cough (weeks)</th>
<th>TB classification (2)</th>
<th>Patient Category (3)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>M</td>
<td>F</td>
<td>04 5-14 15+</td>
<td>Gua Hosp HC</td>
<td>P EP</td>
<td>New Relap RAD Fail Oth</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

### PAGE TOTALS

- **M**: 0-4 5-14 15+
- **F**: 0-4 5-14 15+
- **P EP**: New Relap RAD Fail Oth

### Notes

1. **DOT Option**
   - **Gua**: Guardian
   - **Hosp**: Hospital
   - **HC**: Health centre

2. **TB Classification**
   - **P**: Pulmonary TB
   - **EP**: Extra-pulmonary TB

3. **Patient Category**
   - **New**: New patient, never previously TB-treated
   - **Relap**: Relapse-patient; previously TB-treated and considered cured but now has TB again
   - **Return after default**: Patient starting treatment again after failure; patient starting treatment again after treatment
   - **Other**: Situations different from the 4 mentioned above

**Version 3** March 2008
# Tuberculosis Register

<table>
<thead>
<tr>
<th>Sputum examination</th>
<th>Treatment Outcome (record outcome date)</th>
<th>HIV Test Status (update from latest entry on card)</th>
<th>ARV-Status</th>
<th>CPT-Status</th>
<th>Remarks</th>
</tr>
</thead>
</table>
**Mulanje DH: Quarterly Report**

<table>
<thead>
<tr>
<th>Category</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number TB cases registered</td>
<td>340</td>
</tr>
<tr>
<td>Number TB cases HIV tested</td>
<td>275</td>
</tr>
<tr>
<td>Number TB cases HIV+ve</td>
<td>192</td>
</tr>
<tr>
<td>Number HIV+TB cases on CPT</td>
<td>186</td>
</tr>
<tr>
<td>Number HIV+TB cases on ART</td>
<td>165</td>
</tr>
</tbody>
</table>
Step 7: Empower patients
Patient empowerment on HIV care for HIV-associated TB