HIV and TB - the deadly duo
-the role of HAART

U G Laloo
Enhancing Care Initiative KZN+
Nelson R Mandela School of Medicine
College of Health Sciences
TB HIV fact sheet

- High prevalence of TB in HIV infected groups
- TB is the only proven HIV related infection transmitted from person to person
- TB is curable
- TB is preventable in HIV infected
- TB accelerates the course of HIV
### The Stop TB Strategy at a glance

#### THE STOP TB STRATEGY

<table>
<thead>
<tr>
<th>VISION</th>
<th>A TB-free world</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOAL</td>
<td>To dramatically reduce the global burden of TB by 2015 in line with the Millennium Development Goals and the Stop TB Partnership targets</td>
</tr>
</tbody>
</table>
| OBJECTIVES | • Achieve universal access to quality diagnosis and patient-centred treatment  
• Reduce the human suffering and socioeconomic burden associated with TB  
• Protect vulnerable populations from TB, TB/HIV and drug-resistant TB  
• Support development of new tools and enable their timely and effective use  
• Protect and promote human rights in TB prevention, care and control |
| TARGETS | • MDG 6, Target 6.c: Halt and begin to reverse the incidence of TB by 2015  
• Targets linked to the MDGs and endorsed by Stop TB Partnership:  
  - 2015: reduce prevalence of and deaths due to TB by 50%  
  - 2050: eliminate TB as a public health problem |

#### COMPONENTS

1. Pursue high-quality DOTS expansion and enhancement
   a. Secure political commitment, with adequate and sustained financing  
   b. Ensure early case detection, and diagnosis through quality-assured bacteriology  
   c. Provide standardized treatment with supervision, and patient support  
   d. Ensure effective drug supply and management  
   e. Monitor and evaluate performance and impact

2. Address TB/HIV, MDR-TB, and the needs of poor and vulnerable populations
   a. Scale-up collaborative TB/HIV activities  
   b. Scale-up prevention and management of multidrug-resistant TB (MDR-TB)  
   c. Address the needs of TB contacts, and of poor and vulnerable populations
Risk of developing TB with HIV

- HIV- : lifetime risk of 10%
- HIV+ : risk of 10% per annum
  - Risk of activation 80-200X
- In KwaZulu Natal, South Africa:
  - almost 2/3 TB cases are HIV+
The pathogenesis of TB and interactions with HIV

- TB bacillus
- CD4 T-Lymphocyte
- IFg
- IL-12
- TNF
- IL-1
- Macrophage
- Granuloma
- Monocytes
- Enhanced Viral replication
- NF Kappa B
- Enhanced Viral replication
FIGURE 1
Estimated TB incidence rates, 2008

Estimated new TB cases (all forms) per 100,000 population:
- 0-24
- 25-49
- 50-99
- 100-299
- 100-299
- ≥300
- No estimate
FIGURE 2
Estimated HIV prevalence in new TB cases, 2008

HIV prevalence in new TB cases, all ages (%)

- 0-4
- 5-19
- 20-49
- ≥50
- No estimate
TB notification rate in 20 African countries* versus HIV prevalence in sub-Saharan Africa, 1990–2004


- Consistently reporting each year: Algeria, Angola, Botswana, Cameroon, Comoros, Congo, Côte d'Ivoire, Democratic Republic of Congo, Ghana, Guinea, Kenya, Malawi, Mauritius, Mozambique, Nigeria, Senegal, South Africa, Uganda, United Republic of Tanzania, Zimbabwe
Global epidemiology

• 709 000 HIV+ TB cases
• 85% in sub-Saharan Africa
• TB incidence 8.3X higher in HIV+ Africans

WHO 2008
Future scenarios

• No intervention
  - Cumulative case load of 3.5mill over next 10 years

• Successful HIV control – 20% prevalence, no change in TB control
  - 2.5X increase in TB case load

• Optimal HIV control, cure rate of 80% of TB
  - TB epidemic halved in 5 years

• Effective HIV and TB control
  - TB incidence lower than 1995
1. Standardised national eligibility criteria for starting ART regimens for Adults and Adolescents

<table>
<thead>
<tr>
<th>Eligible to start ART</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ CD4 count ≤200 cells/mm³ irrespective of clinical stage</td>
</tr>
<tr>
<td>▪ CD4 count ≤350 cells/mm³</td>
</tr>
<tr>
<td>▪ In patients with TB/HIV</td>
</tr>
<tr>
<td>▪ Pregnant women</td>
</tr>
<tr>
<td>▪ WHO stage IV irrespective of CD4 count</td>
</tr>
<tr>
<td>▪ MDR/XDR irrespective of CD4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Require fast track (i.e. ART initiation within 2 weeks of being eligible)</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ Pregnant women eligible for lifelong ART</td>
</tr>
<tr>
<td>▪ Patients with very low CD4 (&lt;100)</td>
</tr>
<tr>
<td>▪ Stage 4, CD4 count not yet available</td>
</tr>
<tr>
<td>▪ MDR/XDR TB</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Not yet eligible for ART</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ Transfer to a wellness programme for regular follow up and repeat CD4 testing 6-monthly.</td>
</tr>
<tr>
<td>▪ Advice on how to avoid HIV transmission to sexual partners and children</td>
</tr>
<tr>
<td>▪ Initiate INH prophylaxis if asymptomatic for TB</td>
</tr>
<tr>
<td>▪ Contraceptives and annual Pap smear</td>
</tr>
<tr>
<td>1st Line</td>
</tr>
<tr>
<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td>All new patients needing treatment, including pregnant women</td>
</tr>
<tr>
<td>Currently on d4T based regimen with no side-effects</td>
</tr>
<tr>
<td>Contraindication to TDF: renal disease</td>
</tr>
<tr>
<td>2nd line</td>
</tr>
<tr>
<td>Failing on a d4T or AZT-based 1st line regimen</td>
</tr>
<tr>
<td>Failing on a TDF-based 1st line regimen</td>
</tr>
<tr>
<td>Salvage</td>
</tr>
<tr>
<td>Failing any 2nd line regimen</td>
</tr>
</tbody>
</table>
CAMELIA Study

- 661 TB/HIV adults
  - CD4 <200 (72%<50)
  - 2 week vs 8 week HAART
- 59/332 vs 90/329 died
  - P<0.007
- More IRIS in early HAART

Blanc et al, IAS Vienna 2010
Timing of Initiation of Antiretroviral Drugs during Tuberculosis Therapy

3301 Patients were assessed for eligibility

1970 Were excluded
  794 Were HIV-negative
  627 Declined HIV testing
  349 Did not return for screening visit
  200 Had other reasons

1331 Were screened

689 Were excluded
  130 Did not return for randomization
  101 Responded after enrollment window
  100 Returned for enrollment when enrollment was not open
  91 Did not have confirmed positive smear for acid-fast bacilli
  55 Had CD4+ count >500 cells/mm³
  44 Declined participation
  38 Had medical reasons
  17 Planned to relocate
  17 Had practical reasons
  16 Declined antiretroviral therapy
  13 Were receiving antiretroviral therapy
  12 Had no sputum test
  10 Died
  6 Were not receiving tuberculosis treatment
  3 Were pregnant or planned pregnancy
  36 Had other reasons

642 Underwent randomization
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Integrated Therapy (N = 343)</th>
<th>Sequential Therapy (N = 171)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Repeated Therapy of Tuberculosis (N = 116)</td>
<td>First Episode of Tuberculosis (N = 227)</td>
</tr>
<tr>
<td>Tuberculosis cure†</td>
<td>67 (57.8)</td>
<td>131 (57.7)</td>
</tr>
<tr>
<td>Successful completion‡</td>
<td>16 (13.8)</td>
<td>42 (18.5)</td>
</tr>
<tr>
<td>Therapy success (cure plus successful completion)</td>
<td>83 (71.6)</td>
<td>173 (76.2)</td>
</tr>
<tr>
<td>Died before completion of therapy</td>
<td>7 (6.0)</td>
<td>12 (5.3)</td>
</tr>
<tr>
<td>Therapy interruption</td>
<td>2 (1.7)</td>
<td>3 (1.3)</td>
</tr>
<tr>
<td>Therapy failure§</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Loss to follow-up</td>
<td>13 (11.2)</td>
<td>13 (5.7)</td>
</tr>
<tr>
<td>Therapy outcome unknown because of transfer to another clinic</td>
<td>1 (0.9)</td>
<td>5 (2.2)</td>
</tr>
<tr>
<td>Other outcome</td>
<td>1 (0.9)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Outcome pending (still receiving therapy at time of analysis)</td>
<td>9 (7.8)</td>
<td>20 (8.8)</td>
</tr>
</tbody>
</table>
Figure 2. Kaplan–Meier Survival Curves.
TB denotes tuberculosis.
A5221

- Immediate vs deferred HAART with CD4<200.
- Multinational, multicentre
- Truvada + efavirenz/nevirapine
- Fully enrolled - 800 patients
Challenges and controversies

- Choice of drugs
- 2\textsuperscript{nd} line ARVs
- IRIS
- Drug toxicities
- Drug resistant TB and HAART
- New TB drugs?
- Early mortality on HAART
  - Will empiric TB treatment work?
- Is the strategy viable in rural settings?
Figure 1. Means CD₄ cell counts between the two treatment groups by on-treatment analysis.
Nevirapine vs Efavirenz in TB

- Cohort study in South Africa 2001-6
- 2035 efavirenz, 1935 nevirapine (1075 have TB)
- No difference HIV RNA on efavirenz in TB vs non TB
- HIV RNA failure 2 fold higher on nevirapine in TB vs non TB
- No difference between TB vs non-TB in nevirapine for TB incident cases

Boulle, JAMA, 2008
CAMELIA: Rifampin effect on EFZ levels

• Start ART at 2 weeks vs. 2 months after TB therapy
• All patients receiving rifampin (10 mg/kg) and EFZ 600 mg QD (plus stavudine/lamivudine)
• EFZ assayed by HPLC (N=90), 12 hrs after last dose
  - LLQ 50 ng/ml
  - Therapeutic range 1000-5000 ng/ml
  - Day to day QC variability less than 15%

Chou et al, IAS 2008, Abstract TUPE0085
CAMELIA: PK results

• “Few” pts with EFV < 1000 ng/ml
  - “some” found to not be taking ART
• 1 pt with EFV < 1000 ng/ml at 45 weeks
• 15.7% with levels > 8000 ng/ml
• EFV levels only correlated with body weight at week 18

SUPPORTS NOT DOSE ADJUSTING EFAVIRENZ WITH RIFAMPIN

Chou et al, IAS 2008, Abstract TUPE0085
Challenges

• Preferred co-treatment regimen for HIV-related TB in RLS is rifampin-based anti-TB therapy with EFV-based ART.
  - Not all patients with HIV-related TB can be treated with this regimen.
• Virologic failure of 1st line ART (NVP or EFV + 2 NRTIs) is estimated at 2%-4% per year in RLS
• In RLS → High endemic rates of TB; limited access to rifabutin and need for RIF-based TB treatment; limited access to 2nd line drugs with LPV/r being the cornerstone
Challenges and controversies

• RIF markedly decreases plasma concentrations of all of the available PIs, particularly ATV/r and LPV/r, the two agents most widely available in high TB-burden countries.

• High doses of RTV (up to 400 mg twice-daily) can overcome the PK effect of RIF on PIs i.e. “super-boosted” PIs but poorly tolerated in health volunteers.

• LPV/r 800 mg/200 mg BID (double-dose) better tolerated, but not evaluated in HIV-infected adults with active TB.
Rationale for A5290

- Designed to address several urgent and practical questions for TB endemic countries with large HIV-infected populations:
  - What is the best approach to treatment in patients requiring HIV PIs in the setting of TB treatment?
  - Is the efficacy of RIF and RBT similar in patients treated with dose adjusted LPV/r regimens?
  - Does the addition of an integrase inhibitor improve the outcome of anti-HIV treatment in patients receiving a PI-based regimen with a rifamycin?
Study Design: A5290

- Treatment arms:
  - Arm A: LPV/r 400 mg/100 mg BID + 2 NRTIs + INH/RBT (150 mg 3x/wk)/EMB/PZA x 24 weeks
  - Arm B: LPV/r 800 mg/200 mg BID + 2 NRTIs + INH/RIF/EMB/PZA x 24 weeks
  - Arm C: LPV/r 400 mg/100 mg BID + 2 NRTIs + raltegravir 400 mg BID + INH/RBT (150 mg 3x/wk)/EMB/PZA x 24 weeks

- After completion of TB treatment, ARVs will revert to standard dosing through week 48
Reduction of TB incidence with IPT

- **Kenyan cohort**: IPT initiated in 33% of adults in HIV cohort
  - Prescribed IPT in 9633 who screened negative for TB
  - 76% completed IPT
  - Active TB Incidence at 2 years
    - Complete vs Incomplete IPT: 4.6% vs. 7.7% (HR 2.2)

- **Brazil and Thai cohorts** with similar findings

Diero MOAB0306, Faria de Silva WEPE0159, Phanuphak MOPDB202
TB risk on ART

- **TASO Uganda cohort**: 106K pts
  - 7,000 (6.7%) w/ TB, 866 (12%) on ART, 6279 (88%) not on ART
  - 1622 (23%) cases before ART, 583 (8%) after ART
  - TB prevalence: on ART 0.5%, not on ART 5.9% (p=0.00)

- **NA-ACCORD, IeDEA**: TB risk in first 3 months of ART
  - First 3 months ART 162/100k py, After 3 months 84/100K py
  - Risk factors in first 3 months: lower CD4 (54 vs 138), higher VL (690K vs 72K)
  - No difference by race, sex, site of diagnosis, culture status, ART regimen in early vs. later cases

Lyavala Tasilima MOPE0344, Sterling MOAB0304
TB and HIV opportunities

- Combined programs
  - Provides synergies
    - Improved TB outcomes
    - Improved HIV outcomes
    - Economy of scale
    - Staff rationalization
**Sizonqoba Outcomes**

**HIV**
Change in CD4 & Viral Load over 12 Months

- Mean CD4 Count (cells/mm³)
- Mean Viral Load (copies/ml)

**TB**
99 of 119 (83%) patients successfully completed 6-9 months of TB treatment

**SURVIVAL**
Survival on ARV Therapy

- Days of Follow-up on ARV

![Graphs showing changes in CD4 and viral load, and survival on ARV therapy with TB treatment success rates.]
IRIS

- Increased risk with early HAART
- Benefits outweigh risks of IRIS
- Clinical vigilance
- Management strategies
  - Treatment
  - Patient information
Drug resistant TB and HAART

• No systematic study
• Clinical experience:
  - Similar issues to drug sensitive TB
• High mortality in X-DR TB despite HAART
Fig. 1 Epochs in TB and antituberculous drug development. *DOTS* directly observed therapy, *MDR* multidrug resistant, *MTB* *Mycobacterium tuberculosis*, *TB* tuberculosis, *XDR* extensively drug resistant.
Conclusions

• TB treatment and HAART viable
  - No longer equipoise
• Regimens well described
• IRIS not a reason for concern
• 2\textsuperscript{nd} line HAART a challenge
• Drug resistant TB and HAART
  - No systematic data
The White Plague

Yet the captain of all these men of death that came against him to take him away was consumption, for it was that that brought him down to the grave.

The life and death of Mr. Badman, presented to the world in a familiar dialogue between Mr. Wiseman and Mr. Attentive

John Bunyan, 1680