HIV and TB

Dr. Edmund Wilkins
Head of the HIV Clinical Trials Unit
North Manchester General Hospital
“Support needing populations through medical assistance and the transfer of knowledge to local medical practitioners.”

Our vision for the Medical Assistance & Medical Education (MAME) Programs
Talks – brief!

• Epidemiology
Some of the many challenges that remain

- Epidemiology
TB/HIV current situation: Testing for HIV in patients with TB

Number of countries offering HIV testing for TB patients

62/199

Number of countries reported to WHO

7/210

Number of incident TB cases reported (millions)

3.0 M

2002

3.7 M

2003

4.4 M

2004

9.0 M

2014

92/199

Epidemiology…

• In 2013, 6.1 million TB cases were reported to WHO.
• Of the estimated 9 million people who developed TB in 2013, more than half (56%) were in the South-East Asia and Western Pacific Regions.
• An estimated 1.1 million (13%) of the 9 million people who developed TB in 2013 were HIV-positive.
• Globally, the TB mortality rate fell by an estimated 45% between 1990 and 2013 and the TB prevalence rate fell by 41% during the same period.
Epidemiology…

• 48% of TB patients globally had a documented HIV test result

• In 2013, 70% of TB patients known to be HIV-positive were on ART.

• In 2013, the treatment success rate continued to be high at 86% among all new TB cases.

• By June 2014, 108 countries had access to Xpert MTB/RIF at concessional prices
Estimated TB incidence 2013
TB mortality in HIV
Factors Increasing the Risk of Tuberculosis

• HIV (800 x)
• Silicosis
• Immunocompromise
• Malignancy
• Insulin-dependent diabetes mellitus
• Chronic renal failure
• G-I disease associated with malnutrition

1. Especially lymphoma, leukaemia
2. Gastrectomy, jejunoileal bypass, Ca pancreas, malabsorption

• Age (children > young adults)
• First generation immigrants from high prevalence countries
• Close contacts of patients with smear-positive pulmonary tuberculosis
• CXR evidence of self-healed tuberculosis
• Primary infection < 1 year previously
TB follows HIV

2006 - 709,000 co-infected
85% in Africa
South African Miners Cohort – Cumulative hazard estimate of TB incidence by HIV status

Years since first negative test or since seroconversion

Proportion with TB

HIV +

HIV -

Sonnenberg JID 2005
TB/HIV situation

9% HIV-infected patients had PTB
(5% undiagnosed)

Case finding proportions for HIV- TB = 0.67
and for HIV+ TB = 0.37

Lawn SD. IAS 2007;SUSA501.
Outcome of exposure to MTB – HIV negative

Exposure

- No infection 90%
- Infection 10%

Infection 10%

- Primary active TB 5%
- Continued latent TB

Latent TB 95%

- Reactivation of TB 10% per lifetime
<table>
<thead>
<tr>
<th>Time from infection</th>
<th>Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-8 weeks</td>
<td>Primary complex, positive tuberculin skin test</td>
</tr>
<tr>
<td>3-6 months</td>
<td>Meningeal, miliary and pleural disease</td>
</tr>
<tr>
<td>Up to 3 years</td>
<td>Gastro-intestinal, bone and joint, lymph-node disease</td>
</tr>
<tr>
<td>Around 8 years</td>
<td>Renal tract disease</td>
</tr>
<tr>
<td>From 3 years onwards</td>
<td>Post-primary disease due to reactivation or re-infection</td>
</tr>
</tbody>
</table>

Adapted from Grange JM in Clinical Tuberculosis 1998. Editor PDO Davies
Outcome of exposure to MTB – HIV positive

Exposure

- No infection 80%
- Infection 20%

Infection 20%

- Primary active TB 30%
- Continued latent TB
- Reactivation of TB 10% annually

No infection 80%

Reinfection with new strain: 50:50 vs. 90:10

Latent TB 70%
Also in PTB with lower CD4 ….

• Less often ‘chest’ presentation
• Reduced smear-positive rates: 40% vs. 70%
• Less cavitation
• Increased disseminated disease and extra-pulmonary infection: > 60% vs <20%
• More ‘covert/subclinical’ disease → IRS
• More reactions to all TB drugs
• More MDRTB and higher mortality rate
Opportunistic diseases in the course of HIV-infection

Seroconversion:
- Acute retroviral syndrome

CD4+ (cells/µL)

Years after infection

Oral Candida-infection
- Kaposi sarcoma
- Lymphoma
- Dementia
- Oral haircell-leukoplakia

Pneumococcal pneumonia
Candida vaginitis
- ITP

Cachexia
- Toxoplasmosis
- PCP
- HSV
- Candida esophagitis
- Cryptococcosis

TB

CMV
Radiological features of HIV+ patients

Cavitatory TB
CD4+ 510 (23%)

Miliary TB
CD4+ 194 (18%)

Disseminated TB
CD4+ 34 (8%)
Pulmonary vs extra-pulmonary TB: HIV+ vs HIV-
Patient AB – high CD4

• 43yr old heterosexual male; engineer contracted to Nigeria
• Several local partners: unsafe sex
• Admitted with fever, weight loss 6m, pain on swallowing and diarrhoea
• Increasing productive cough and breathlessness
• O/E: temp 38.5oC, cachectic, OCP, generalised lymphadenopathy, hepatosplenomegaly
Patient AB

- CXR:
- HIV +ve
- Induced sputum:
  - PCP –ve
  - AFB +ve
- Blood cultures –ve
- Absolute LC count 0.9
- CD4 320 cells/ml
Differential diagnosis

• **TB**

  • Bacterial (staphylococcal/klebsiella)
  • Atypical mycobacterium
    • MAI
    • Mycobacterium kansasii
  • Rhodococcus equi
  • Meliodosis
  • Nocardiosis
  • Cryptococcus
  • Aspergillus
CXR manifestations of Pulmonary TB

Major
• Collapse/ Consolidation
• Cavitation
• Mediastinal lymphadenopathy
• Miliary
• Pleural effusion

Less Common
• Pneumothorax
• Loculated empyema
• ARDS
• Cor Pulmonale
• Localised emphysema
### Differential Diagnosis Of TB-related Pulmonary Disease: Chest X-ray Findings

<table>
<thead>
<tr>
<th>Appearance</th>
<th>Major causes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diffuse infiltrate</strong></td>
<td><em>Pneumocystis jirovecii (carinii)</em> pneumonia, tuberculosis, Kaposi’s sarcoma, non-Hodgkin lymphoma, atypical bacterial pneumonia, viral pneumonitis</td>
</tr>
<tr>
<td><strong>Cavitations</strong></td>
<td>TB, Nocardia, Rhodococcus, bacterial pneumonia, aspergillus</td>
</tr>
<tr>
<td><strong>Nodules/focal consolidation</strong></td>
<td>Tuberculosis, Kaposi’s sarcoma, non-Hodgkin lymphoma <em>Cryptococcus, Histoplasma</em></td>
</tr>
<tr>
<td><strong>Hilar lymphadenopathy</strong></td>
<td>Tuberculosis, Kaposi’s sarcoma, non-Hodgkin lymphoma <em>Cryptococcus, Histoplasma</em></td>
</tr>
<tr>
<td><strong>Pleural effusion</strong></td>
<td>Kaposi’s sarcoma, tuberculosis, pyogenic bacterial pneumonia, primary effusion lymphoma</td>
</tr>
</tbody>
</table>
Patient BC – low CD4

- 37y-old White French born ex-IDU for 8y
- Lived in Spain till 2005, travelled Asia/Europe ++
- PMH – pulmonary TB 1998, HCV +ve
- Presented with 6w history of fever, sweats, loss of weight
- HIV+ve, CD4 28 cells/mm3, VL 295,000 c/ml
- On methadone
Chronology of symptoms–patient BC
Causes of PUO in late stage HIV

• **Common:**
  - TB
  - MAI
  - Lymphoma

• **Less common:**
  - PCP
  - Salmonellosis
  - Syphilis
  - CMV
  - Cryptococcus
  - IRIS

• **Rare UK:**
  - Histoplasmosis
  - Penicilliosis
  - Leishmaniasis
  - Bartonellosis
  - Coccidiodomycosis
  - Toxoplasmosis
  - Castleman’s disease
  - Haemophagocytic syndrome
Patient BC

- AFB +ve:
  - Induced sputum
  - Lymph node biopsy
  - Bone marrow

- Covered for both MTB and MAI

- Mycobacteria isolated
  - Blood and tissues above

- TB identified – RIF probe -ve
Pulmonary TB

HIV –ve
HIV +ve CD4 >500
AFB +++ve/culture +ve

HIV +ve
CD4 200-500
AFB scants/culture +ve

HIV +ve
CD4 <200
AFB –ve/culture +ve
Identifying E-P and disseminated TB

No major differences between HIV+ve and HIV -ve
General rules

- In a patient with E-P TB HIV is more likely
- Occurs at younger age and often subclinical
- Often part of disseminated or multiple site disease or visceral disease
- If low CD4:
  - AFB +ve more common in biopsies
  - Mycobacteraemia more common
  - No granulomata / may present as IRS
- Often more difficult to manage
TB meningitis
TB meningitis
TBM: HIV +ve vs. HIV -ve

• No differences:
  • Clinical presentation
  • CSF findings
  • Blood parameters
  • Frequency of miliary picture
  • Neuroimaging abnormalities

• Significant difference:
  • Rate of AFB positivity CSF
  • Presence of extra-meningeal disease
  • Morbidity and mortality
TB spine
TB pericarditis
HAART is life saving in TB co-infected
Mortality among patients with prevalent active TB (n=73) initiating ART

No difference in CD4 count or Stage 4 disease between those starting and not starting

Lawn S et al. CROI 2007;Abstract 81
But do you need to / when to Start ART?

CD4<350
Or ?<200
Or ?<100

TB TREATMENT

1  2  6

Months

ANTIRETROVIRAL THERAPY-WHEN?
Potential Benefits and Risks of Starting ART Immediately With TB Treatment

**Benefits**

- Reduced morbidity\(^1,2\)
- Reduced mortality\(^1,2\)
- Improved TB outcome

**Risks**

- Increased toxicity to TB and ART therapy\(^3\)
- Drug interactions between HIV and TB medications\(^3\)
- Pill burden
- Immune Reconstitution Syndromes (IRS)\(^4\)

\(^1\) Dean, AIDS, 2002; \(^2\) Pedral-Sampaio, 2004, Brazil JID; \(^3\) Harries, Lancet, 2006; \(^4\) Lawn, Lancet ID, 2005
4 key studies on TB

- **CAMELIA** Cambodia PTB <500
- **SAPIT** South Africa PTB <200
- **STRIDE** 4 Continents PTB <250
- **NCT00433719** Vietnam TBM
CAMELIA strategy: CD4 <200: 2w vs. 8w?

- **ARV D4T-3TC-EFV**
  - **Early**
    - TB treatment
    - 2HRZE/4HR
  - **Late**
    - TB treatment
    - **ARV D4T-3TC-EFV**

Switch D4T to AZT

**Legend**
- Rd: Randomization
- H: isoniazid
- Z: pyrazinamide
- R: rifampicin
- E: ethambutol
- D4T: stavudine
- 3TC: lamivudine
- EFV: efavirenz

**Study Timeline**
- Day 0
- Week 2
- Week 8: 2 months
- Week 26: 6 months
- Week 50: 12 months
- Week 58: 18 months
- Week 78: Follow-up (every 6 months after week 78)

**Study References**
- ANRS 1295/12160 - CIPRA KH001/10425 study
Log-rank p-value: $p = 0.0042$

<table>
<thead>
<tr>
<th>Survival probability (95% CI)</th>
<th>Early arm</th>
<th>Late arm</th>
<th>Log-rank p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 50</td>
<td>86.1 (81.8 – 89.4)</td>
<td>80.7 (76.0 – 84.6)</td>
<td>0.07</td>
</tr>
<tr>
<td>Week 100</td>
<td>82.6 (78.0 – 86.4)</td>
<td>73.0 (67.7 – 77.6)</td>
<td>0.006</td>
</tr>
<tr>
<td>Week 150</td>
<td>82.0 (77.2 – 85.9)</td>
<td>70.2 (64.5 – 75.2)</td>
<td>0.002</td>
</tr>
</tbody>
</table>
SAPIT Study: Mortality in sequential arm occurred late

Sept 2008: DSMB arm of the SAPIT trial stopped

Reduction in mortality rates was present in patients with CD4 counts above and below 200 cells/mm³
SAPIT Study: Mortality in sequential arm occurred late

Sept 2008: DSMB arm of the SAPIT trial stopped

Kaplan-Meier curve for AIDS or death in patients with CD4 <50 cells/mm³

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

68% reduction of AIDS / death (p=0.06)
A5221: STRIDE – study design

Presumed or confirmed TB; EFV TDF FTC: RIF based country approved regimen: <2w or 8-12w. 806 patients from 4 continents, Half had confirmed TB, Median CD4 77, Median 10d and 70d
More OI’s and TB deaths in the early arm
## When to start HAART (BHIVA 2009)

<table>
<thead>
<tr>
<th>CD4 count</th>
<th>When to start</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 100</td>
<td>As soon as practical</td>
</tr>
<tr>
<td>100 - 350</td>
<td>As soon as practical, but can wait until 2 months of TB Rx, especially if difficulties with toxicity / adherence</td>
</tr>
<tr>
<td>&gt; 350</td>
<td>At physician discretion</td>
</tr>
</tbody>
</table>
Is there enough evidence to give clear guidance on what level of CD4 and when into TB treatment one should start HAART?

NO – but don’t wait until it’s too late
Rifampicin

• The major problem is the use of rifampicin with HAART

• But it is an essential part of the solution for TB
## TB-HIV drug interactions

<table>
<thead>
<tr>
<th>Drug</th>
<th>Rif</th>
<th>INH</th>
<th>PZA</th>
<th>Eth</th>
<th>Strep</th>
<th>RBT</th>
<th>RPT</th>
<th>Mox</th>
<th>Ethio</th>
<th>Cyclo</th>
<th>Capreol</th>
</tr>
</thead>
<tbody>
<tr>
<td>SQV/r</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>RTV</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>IDV</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>NFV</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>FPV/r</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>LPV/r</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>ATV/r</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>TPV/r</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>DRV/r</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>NVP</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>EFV</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>ETR</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>ZDV</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>3TC</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>ddi</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>d4T</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>ABC</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>ddC</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>FTC</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>TDF</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>ENF</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>MVC</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>RAL</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
</tbody>
</table>

[www.hiv-druginteractions.org](http://www.hiv-druginteractions.org)
Treatment of drug sensitive TB

- 90% of MTB dead in 2 days when regimen includes INH ✓
- 99% of MTB dead in 14 days when regimen also includes Rifampicin ✓
- If INH and RIF and PZA given in first 2 months then total course of TB treatment is 6 months ✓

- Debate whether HIV + should be treated for longer
- Debate whether use of quinolones could shorten to 4 months
Choices

• NNRTI’s:
  • Nevirapine
  • Efavirenz

• PI/r

• 3NRTI

• New drugs:
  • Raltegravir
  • Maraviroc
  • Etravirine
  • T-20
Nevirapine and rifampicin

• Standard dose?

• Increased dose?

• Problems of Lead in
PK interactions between EFV and rifampicin in HIV patients with TB

• EFV peak, trough and AUC decreased 24%, 25% and 22% in the presence of rifampicin ✓

• Large inter patient variability observed, suggesting use of TDM ✓

• PK of EFV 800 mg plus rifampicin similar to those of EFV 600 mg without rifampicin ✓

• Rifampicin PK did not change substantially in the presence of efavirenz ✓

Body Weight Cutoff for EFV Dosing in Combination with Rifampicin

- 71 patients in Thailand taking anti-TB Rx, initiating HAART with EFV 600mg + d4T/3TC
- EFV concentrations at 12h after dosing at weeks 6 & 12
- High body weight associated with low C12 EFV at weeks 6 & 12
- C12 EFV of 1mg/l at mean weight of 57.5kg
- 60kg weight cutoff appropriate for EFV dose escalation 600 → 800mg
## NNRTIs with anti-TB drugs (BHIVA 2009)

<table>
<thead>
<tr>
<th></th>
<th>Rifampicin</th>
<th>Rifabutin</th>
<th>Clarithromycin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EFAVIRENZ</strong></td>
<td>Efavirenz levels ↓ by 20–30%</td>
<td>Rifabutin levels ↓ by 38%.</td>
<td>No significant interaction</td>
</tr>
<tr>
<td></td>
<td>Efavirenz increased to 800mg daily if weight &gt;60kg</td>
<td>Rifabutin increased to 450mg daily</td>
<td>Use standard doses</td>
</tr>
<tr>
<td></td>
<td>Efavirenz at 600mg daily if weight &lt;60kg</td>
<td>Efavirenz at standard dose</td>
<td>Reports of ↑ rates of rash: consider Azithromycin instead (no interaction)</td>
</tr>
<tr>
<td></td>
<td>Rifampicin at standard dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NEVIRAPINE</strong></td>
<td>Nevirapine levels ↓ 20–55%</td>
<td>Use standard doses but little data so not recommended</td>
<td>No significant interaction</td>
</tr>
<tr>
<td></td>
<td>No change in rifampicin</td>
<td></td>
<td>Use standard doses</td>
</tr>
<tr>
<td></td>
<td>Not recommended</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ETRAVIRINE</strong></td>
<td>No data available but expected ↓↓↓ etravirine</td>
<td>Etravirine levels ↓ 37%</td>
<td>Use with caution</td>
</tr>
<tr>
<td><strong>RILPIVIRINE</strong></td>
<td>TMC-278 levels ↓ 90%</td>
<td>TMC-278 levels ↓ 50%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Do not use</td>
<td>Double dose TMC-278</td>
<td></td>
</tr>
</tbody>
</table>
Choices

- NNRTI’s:
  - Nevirapine
  - Efavirenz

- PI/r

- 3NRTI

- New drugs:
  - Raltegravir
  - Maraviroc
  - Etravirine
  - T-20
Boosted PIs and Rifampicin Interaction

- Ritonavir 400 bid required
- GI toxicity and lipid perturbation
- High rates of elevated transaminase\(^1\) (5/7 dropouts)\(^1\)
- Plus recent PK study\(^2\) - LFT problems

- Early studies from SA suggested could be used
- SQV 1000/rit100 BID\(^3\)
- All patients in this arm experienced grade 4 transaminase elevations\(^3\)

---

1. La Porte et al. AAC. 2004;48(5):1553-1560
# TB Treatment Regimens: Rifabutin

<table>
<thead>
<tr>
<th>HAART</th>
<th>Dose</th>
<th>TB therapy</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTI</td>
<td>No change</td>
<td>RBT</td>
<td>No change</td>
</tr>
<tr>
<td>Boosted PI</td>
<td>No change</td>
<td>RBT</td>
<td>150 mg 2-3/7</td>
</tr>
<tr>
<td>nevirapine</td>
<td>200 mg bd</td>
<td>RBT</td>
<td>300 mg od</td>
</tr>
<tr>
<td>efavirenz</td>
<td>600 mg od</td>
<td>RBT</td>
<td>450 mg od</td>
</tr>
</tbody>
</table>

Anton Pozniak Personal Communication
Choices

- NNRTI’s:
  - Nevirapine
  - Efavirenz
- PI/r
- 3NRTI
- New drugs:
  - Raltegravir
  - Maraviroc
  - Etravirine
  - T-20
Interactions with raltegravir

<table>
<thead>
<tr>
<th><strong>Rifabutin</strong></th>
<th><strong>Rifampicin</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>No dose change required of either drug</td>
<td>The co-administration of 800 mg q12hr RAL with 600 mg qd RIF resulted in a 53% decrease in RAL C12hr relative to 400 mg q12hr RAL alone</td>
</tr>
</tbody>
</table>
BHIVA TB Guidelines

**Boosted PI**
- Rifampicin: Not recommended
- Rifabutin: 150mg x 3 per week, boosted PI dosed as normal

**Integrase inhibitors (raltegravir / elvitegravir)**
- Rifampicin: Do not use / not recommended
- Rifabutin: Use with caution / not recommended

**Entry Inhibitors (Maraviroc / T20)**
- Rifampicin: Not recommended / use standard doses
- Rifabutin: Use standard doses
Treatment

Rifater®
Rifampicin 120 mg
Isoniazid 50 mg
Pyrazinamide 300 mg
Drug therapy

- 1944 Streptomycin
- 1949 PAS
- 1952 Pyrazinamide
- 1954 Isoniazid
- 1955 Cycloserine
- 1962 Ethambutol
- 1963 Rifampicin

- Quadruple therapy:
  - rifampicin + isoniazide + pyrazinamide + ethambutol 2/12
  - Rifampicin + isoniazid 4/12
Patient AB

- CXR:
- HIV +ve
- Induced sputum:
  - PCP –ve
  - AFB +ve
- Blood cultures –ve
- Absolute LC count 0.9
- CD4 320 cells/ml
TB-associated Immune Reconstitution Disease (IRD)

- Retrospective cohort of incidence of IRD in TB patients in first 4 months of starting ARV in South Africa

- IRD developed in 19; 141 did not develop IRD

- IRD occurred in 32% of those who started ART within 2 months of TB diagnosis

- 84% had pulmonary and 37% intra-abdominal IRD

In multivariate analysis, risk of IRD strongly associated with early ARV initiation and CD4 count.

Lawn S et al. CROI 2007;Abstr. 863.
How common is IRIS?
TB-associated IRD

All patients with CD4 <50 cells/mm³ developed IRD if ART initiated in first month
Low risk of death overall (1.3%): mostly self-limiting.

Lawn S et al. CROI 2007; Abstr. 863.
Time to initiation of open label prednisolone

Matched groups at BL apart from length of time from starting TB treatment to starting ART: longer in prednisolone arm

35 patients initiated OL prednisolone; 20 in placebo arm and 15 in prednisolone arm

Meintjes G, et al
Oral Abstract 34
How to manage TB-IRIS

• **Background:** occurs in 8-43%, anecdotal reports steroids beneficial but concerns may worsen KS/CMV

• **Hypothesis:** 4w prednisolone would reduce need for medical interventions, be safe and not ↑ infections

• **Design:**
  - Prednisolone or placebo, randomised double blind
  - 1.5mg/kg for 2 weeks then 0.75mg/kg for 2 weeks
  - Follow-up assessments: 1, 2, 4, 8, and 12 weeks
  - Open-label at physicians’ discretion if clinical deterioration/relapse

• **Primary endpoint:**
  - Cumulative number of days and OPD therapeutic procedures (arbitrarily counted as 1 additional day), ITT analysis

Meintges et al. CROI 2009. Abstract 34
Case definition & enrolment

Case definition: *Prior to ART*
- Evidence of TB
- Initial improvement with TB treatment
- Still on TB treatment
- RIF-sensitive strain

*Within 3m of starting ART*
- New/recurrent TB symptoms
- Presence of ≥1 of: ↑LN, cold abscess, serous effusions, lung infiltrates

287 screened (June 2005-Dec 2007)

- Alternative diagnosis = 44
- Did not fulfil case definition = 65
- Exclusion criterion = 55
- Unwilling/unable to consent = 13

Enrolled = 110

Placebo = 55
- Died (2), defaulted (6), rifampicin resistance (6), discontinued study drug (3)

Prednisolone = 55
- Died (3), defaulted (0), rifampicin resistance (4), discontinued study drug (1)

Exclusion criteria: KS
- Prior ART
- Life-threatening IRIS

Meintges et al. CROI 2009. Abstract 34
Symptom score

Week 2

- Placebo Arm: n = 55
- Prednisone Arm: n = 55

- 43% with Deterioration
- 18% with No Change
- 30% Improved or Resolved

Week 4

- Placebo Arm: n = 48
- Prednisone Arm: n = 54

- 17% with Deterioration
- 4% with No Change
- 56% Improved or Resolved

In relation to week 0

- p = 0.001
- p = 0.03

Meintges et al. CROI 2009. Abstract 34
Chest Radiograph score

In relation to week 0
Independent CXR and USS LN evaluation

In relation to week 0
Independent CXR and USS LN evaluation

Ultrasound score demonstrated no differences at week 2 or 4

Meintges et al. CROI 2009. Abstract 34
## Primary endpoint/AE

### Cumulative number of days and OPD therapeutic procedures (counted as 1 additional day), ITT analysis

<table>
<thead>
<tr>
<th></th>
<th>Placebo arm (n=55)</th>
<th>Prednisolone arm (n=55)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total days hospitalised</td>
<td>463</td>
<td>282</td>
<td></td>
</tr>
<tr>
<td>Total OPD procedures</td>
<td>31</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>Cumulative 1° endpoint (median, IQR)</td>
<td>3 (0-9)</td>
<td>1 (0-3)</td>
<td>0.046</td>
</tr>
</tbody>
</table>

### Death on Study

<table>
<thead>
<tr>
<th></th>
<th>Placebo Arm</th>
<th>Prednisone Arm</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death on Study</td>
<td>2 (4%)</td>
<td>3 (5%)</td>
<td>0.65</td>
</tr>
</tbody>
</table>

### Corticosteroid side effects*

<table>
<thead>
<tr>
<th></th>
<th>Placebo Arm</th>
<th>Prednisone Arm</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroid side effects</td>
<td>18 (33%)</td>
<td>12 (22%)</td>
<td>0.20</td>
</tr>
</tbody>
</table>

### Corticosteroid side effects while on study drug

<table>
<thead>
<tr>
<th></th>
<th>Placebo Arm</th>
<th>Prednisone Arm</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroid side effects while on study drug</td>
<td>3 (5%)</td>
<td>8 (15%)</td>
<td>0.11</td>
</tr>
</tbody>
</table>

### Infections

<table>
<thead>
<tr>
<th></th>
<th>Placebo Arm</th>
<th>Prednisone Arm</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections</td>
<td>30 (55%)</td>
<td>36 (65%)</td>
<td>0.24</td>
</tr>
</tbody>
</table>

### Severe Infections**

<table>
<thead>
<tr>
<th></th>
<th>Placebo Arm</th>
<th>Prednisone Arm</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe Infections**</td>
<td>4 (7%)</td>
<td>2 (4%)</td>
<td>0.40</td>
</tr>
</tbody>
</table>

Meintges et al. CROI 2009. Abstract 34
Conclusions

• Prednisolone reduced need for medical interventions (days hospitalised and outpatients procedures combined)

• Consistent benefit maximal in 1\(^{st}\) 4 weeks:
  – Symptom score, CRP, radiology score, Karnofsky score

• Benefits shown despite crossovers to OL prednisolone

• No excess of steroid complications

• 4 weeks may have been too short and tapering dose probably better
Thank you

For further information please contact:

**Jean-Marc Debricon**
CEO
jm@greenshootsfoundation.org
Mobile: +44 7595 600 766

UK charity number 1138412  US 501(c)(3) registered

**Green Shoots Foundation**
P.O. Box 63678
London, SW11 9BD
UK

General enquiries: info@greenshootsfoundation.org
Website: www.greenshootsfoundation.org