TRANSLATING SCIENCE TO END HIV IN SOUTHERN AFRICA

AIDS 2018 POST-CONFERENCE SYMPOSIUM

Harare, Zimbabwe, 24 June 2019
HIV and TB

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OUTLINE

• The burden of HIV/TB

• Addressing the co-epidemic
  – Diagnosis
  – Treatment: When to start ART in TB infected
  – Shorter treatment regimens

• Prevention
  – Shorter and safer regimens
  – Special populations

• Conclusion
Global TB/HIV Burden

1.6 million TB deaths in 2017

10 million people fell ill with TB

TB is the leading killer of people with HIV

And major cause of death due to antimicrobial resistance

920,000 new cases of TB among people with HIV
But only 51% of cases reported

HIV-Related TB: 30 High Burden Countries

Progress in reducing TB deaths

Tuberculosis Global Report 2018
Zimbabwe HIV country context

- HIV prevalence - 14.6%
- TB prevalence - 221/100,000 pop & TB/HIV co-infection - 63%
- 5-8% of all TB notifications occur in children (<15yrs)
- 4.6% and 14.2% Rifampicin Resistant-TB among new and re-treatment cases respectively
- Strengthened HIV/TB collaboration programs
Addressing the co-epidemic of TB and HIV: Current evidence

- HIV is the most important risk factor for developing TB
- Interaction of TB and HIV is bidirectional and synergistic
- Life time risk of developing TB 20 times in HIV +ve
- High risk of mortality from DR-TB

Global TB Report 2018
Toossi Z. 2003
Diagnosis

- Timely and accurate diagnosis essential for reducing morbidity and mortality in PLHIV
- Smear microscopy – low sensitivity
- Culture - gold standard but results 6-8 weeks
- Radiology – not definitive
- XPert MTB /RIF
- LAM - for very sick patients
- Line Probe Assay

Harries Int J Tuberc Lung Dis 1998
Smith Chest 1994
Mtei clin Infect Dis 2005
Swaminathan Int J Lung Dis 2004
WHO Policy update 2013
Treatment

• Challenges of treating both diseases:
  – Integrating HIV/TB treatment programs
  – High pill burden compromising adherence
  – Overlapping side effects
  – Drug-drug interaction
  – Spectrum of IRIS

Abdul Karim et al AIDS 2004
Chien JW et al Chest 1998
Timing of Treatment

• Current view—diagnose HIV early and start Treatment
• What about co-infection?
• SAPIT, CAMELIA, STRIDE studies
• In the era of test and treat what should we do?

Blanc NEJM 2011,
Havlir D NEJM 2011
Abdool KS NEJM 2010
Treatment (cont)

- Current move is TLD as first regimen
- DDI-reduced exposure to DTG were addressed by doubling the dose of DTG
- The high potency of DTG > IRIS


K Dooley CROI 2018
Shorter TB Treatment Regimens

- Highly potent regimens of shorter duration may facilitate treatment completion
  - Improved individual outcomes
  - Public health outcomes
- ReMox and Oflotub phase 3 treatment shortening studies: did not perform better than the control arm.

Merle et al, 2014
Gillespie et al 2014
A New Phase 3 Rifapentine-based Treatment-Shortening Trial: TBTC Study 31 / A5349

Screen for eligibility

Consent, enroll

Randomize 1:1:1

Regimen 1 (control)
2RHZE/4RH (26 wks)

Regimen 2 (investigational)
2PHZE/2PH (17 wks)

Regimen 3 (investigational)
2PHZM/2PHM (17 wks)

End point: TB-free survival at 18 months after treatment assignment

Protocol Chairs
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TB Preventive Therapy

- Finding and treating active TB is NOT ENOUGH
- WHO has strongly recommended treatment for latent TB-PLWHIV and <5yr HHC
- IPT coverage has remained very low (range 1%-53%)

Global TB Report 2918
ART + IPT For Reducing TB in High Burden Settings

Enhanced Prophylaxis plus Antiretroviral Therapy for Advanced HIV Infection in Africa

A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa

<table>
<thead>
<tr>
<th>Arm</th>
<th>Event %</th>
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<tbody>
<tr>
<td>Early ART+IPT</td>
<td>5.7%</td>
</tr>
<tr>
<td>Early ART</td>
<td>7.4%</td>
</tr>
<tr>
<td>Deferred ART+IPT</td>
<td>8.8%</td>
</tr>
<tr>
<td>Deferred ART</td>
<td>14.1%</td>
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</table>

Early ART vs deferred HR 0.56 (95% CI 0.41-0.760)
IPT vs no IPT HR 0.65 (95% CI 0.48-0.88)

J Hakim et al NEJM 2017
TEMPRANO NEJM 2015
TB Preventive Therapy: Shorter & Safer Regimens

Conclusions of 3HP trials

- Non-inferior (or almost superior) to INH in adults, adolescents and children >2 years
- Safer than INH or RZ, Safe in HIV+
- Better adherence and treatment completion

3HP also safe in HIV+ Sterling AIDS 2016
Ultra-short Course: Once Daily Rifapentine with Isoniazid for 4 weeks (BRIEF TB 1HP trial)

- 3000 HIV+
- Median 3.3 years follow-up
- 3% from USA, rest LMIC
- Median CD4 470
- 54% female
- 43% on EFV, 7% on NVP ART
- 13% CD4<250
- 22% LTBI+

<table>
<thead>
<tr>
<th></th>
<th>1HP</th>
<th>9H</th>
<th>Comparison</th>
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<tbody>
<tr>
<td>TB cases</td>
<td>32 (2.2%) IR 0.65/100PY</td>
<td>33 (2.2%) IR 0.67/100PY</td>
<td>IRD -0.023 95%CI -0.35, 0.3 NON-INFERIOR</td>
</tr>
<tr>
<td>SAEs</td>
<td>5.6%</td>
<td>7.2%</td>
<td>P=0.07</td>
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<tr>
<td>Treatment completion</td>
<td>97%</td>
<td>90%</td>
<td>P&lt;0.01</td>
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Chaisson CROI 2018; Swindells, NEJM 2019
WHO Guidelines for LTBI

- INH 6 months for adults and children
- RIF + INH for 3 months for children and adolescents < 15 yr
- RPT and INH weekly for 3 months for adults and children
### Zimbabwe Treatment options for LTBI

<table>
<thead>
<tr>
<th>On Efavirenz Regimen*</th>
<th>Preferred Regimens</th>
<th>Alternative</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rifapentine + Isoniazid (HP) weekly for 3 months (3HP) [for both children and adults]</td>
<td>Isoniazid</td>
</tr>
<tr>
<td></td>
<td>Rifampicin + Isoniazid (HR) daily for 3 months (3HR) [in children ONLY]</td>
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<table>
<thead>
<tr>
<th>On DTG based regimen*</th>
<th>Preferred Regimens</th>
<th>Alternative</th>
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<tbody>
<tr>
<td></td>
<td>Isoniazid daily for 6 months</td>
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*Those on DTG and PIs **MUST** use only INH for prophylaxis
Special Populations: IPT in pregnancy

1) IMPAACT P1078- Immediate vs deferred IPT
   - Higher than expected AEs attributed at least possibly to INH in both arms

A Gupta CROI 2018
Special Populations: IPT in pregnancy

1) IMPAACT P1078- Immediate vs deferred IPT
   - Higher than expected AEs attributed at least possibly to INH in both arms.
   - Higher adverse pregnancy outcomes in the immediate arm

2) TSHEPISO Cohort-IPT and pregnancy outcomes in HIV+ve women
   - No adverse pregnancy outcomes (27% vs 15% p=0.009)

Salazar Poster#77 CROI 2019
A Gupta CROI 2018
Conclusions

• There is still a very high burden of TB disease globally including HIV/TB disease
  – Zimbabwe is one of the 30 high TB, TB/HIV, MDR TB burden countries

• There is need to search for:
  – better drugs and shorter regimens for TB treatment
  – shorter and safer regimens for TB Prevention
Acknowledgements

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- TBTSG Leadership
- A. Gupta (slides)
- S31/A5349 Study Team
- Milton Park CRS Team
Are we going to see

THE END OF TB

in our lifetimes?

A call from the millennium children of the Eastern Mediterranean Region

World Health Organization