Catalysing HIV/TB research: innovation, funding and networking.


University of Cape Town Medical School, Cape Town, South Africa.

CHALLENGES ON TUBERCULOSIS AND HIV RESEARCH.

Françoise BARRÉ-SINOUSSI,
Institut Pasteur, France
Global burden: estimation of 1.37 million new cases of HIV-TB in 2007 (15% of the total global burden of TB).

456 000 HIV-TB deaths accounted for 23% of global HIV/AIDS mortality.

Sub-Saharan Africa: 79% of the disease burden.

South Africa alone: accounts for over one quarter of all cases.

Increased frequency of:
- smear negative  (Corbett, CID 2002)
- extra-pulmonary TB  (Ackah, Lancet 1995)
- non specific radiological abnormalities  (Tshibwabwa-Tumba, J Radiol 1997)

More non diagnosed and non treated TB

More deaths
(Kramer, Am J Med 1990)
(Rana JAIDS 2000)

Treatment

More deaths
(Ackah, Lancet 1995)
(Harries, Lancet 2001)

Cured

PDR-TB
MDR-TB
XDR-TB

More recurrence
(Korenromp, CID 2003)

20% of PLWH on HAART died of TB...
Clinical and basic Research :
At least 4 research priorities

- Improve TB diagnosis in HIV-infected patients, especially in children / extrapulmonary TB

- Improve treatment strategy in both disease

- Better understand the pathophysiology of IRIS to improve its diagnosis/prognosis and treatment

- Implement isoniazid preventive therapy, esp. in high-prevalence settings and develop new preventive measures
NEED TO IMPROVE TB SCREENING

**Current**

- Symptoms and Chest X Ray (Clinical)
- Sputum smear / Culture / PCR (bacteriologic)
- Tuberculin test (immunologic)
- IGRA (immunologic)
  - Quantiferon; T Spot

**Future**

- Bacteriologic: Frequently fails, notably in diagnosing extra-pulmonary TB.
- Immunologic: Fails to distinguish latent infection from active disease

- Differential diagnosis of latent infection and active disease
- Predictive diagnosis of disease susceptibility.
- Added value:
  - Monitoring of drug and vaccine trials.
  - Identification of novel targets for rational vaccine and drug design.
IMPROVE TB DIAGNOSIS

Data on TST vs IGRA and/or combined TST-IGRA in HIV patients:

105 naïve HIV-TB patients in India.
Quantiferon-TB GOLD: Pos. in 65%, Indeterm. in 17%, Neg. in 18%.

But Discordant Reports on IGRA:
⇒ Reasonable vs insufficient sensitivity
⇒ Insufficient specificity

Role of Interferon Gamma Release Assay in Active TB Diagnosis among HIV Infected Individuals

Basirudeen Syed Ahamed Kabeer¹, Rajasekaran Sikhamani⁵, Sowmya Swaminathan², Venkatesan Perumal³, Paulkumaran Paramasivam⁴, Alamelu Raja¹*


Review by T.Mori in

DOI 10.1007/s10156-009-0686-8
NEED TO IMPROVE TB DIAGNOSIS

Needs for further studies and for new tools in particular for:

**Extra-pulmonary TB:**
- biological markers in serum / fluids (e.g., ADA in pleural fluid)
- improve BK detection when bacilli load is low

**Children: TB diagnosis, a difficult challenge, specially in HIV+**
- TB in children differs from TB in adults (More extra-pulmonary forms; Adult forms only in older children; Rare bacteriological confirmation)
- In HIV+ children: non specific clinical and radiological features with difficulties to differentiate from other pulmonary infections.
• Can we improve the performance of the tests we use?
  – **Immunodiagnosis:** TST by IGRAs?

• Can we do better to improve AFB detection and MTB culture with simpler and quicker methods?
  – **Sampling methods:**
    • Induced sputum
    • Nasopharyngal aspirate
    • String test
  – **Direct detection**
    • Auramine and fluorescence microscopy
    • PCR
  – **Culture**

• Can we improve the scoring systems?
NEED TO IMPROVE TREATMENT STRATEGY

Current challenges: High pill burden, overlapping drug interactions and toxicities, IRIS / PR, adherence challenge, MDR/XDR...

Ongoing and Future: Several strategy trials ongoing and/or needed.

Two strategic questions in adult patients:

- Which TB and/or HAART regimen?
- When to start HAART?
WHICH HAART REGIMEN?

- 2 NRTIs + 1 PI
- 2 NRTIs + 1 NNRTI (incl. generics in low-income settings)
- 3 NRTIs

No large prospective randomized clinical trials published yet, but data expected in 2009-2011 on:

⇒ Efficacy of a once-daily HAART regimen?
  ⇒ BKVIR-ANRS 129 (Truvada+EFV)

⇒ Nevirapin or efavirenz?
  ⇒ NVP/EFZ Thai and Indian studies
  ⇒ NVP/EFZ Mozambique (CARINEMO-ANRS study)

⇒ Raltegravir + Tenofovir?
  ⇒ Reflate TB-ANRS 12180 Brazil
### WHEN TO START HAART? EARLY OR LATE?

<table>
<thead>
<tr>
<th>START TB TREATMENT AND HAART SIMULTANEOUSLY</th>
<th>START TB TREATMENT FIRST AND DELAY HAART</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PROS</strong></td>
<td><strong>PROS</strong></td>
</tr>
<tr>
<td>Lower risk of HIV disease progression or death in advanced patients (CD4 &lt; 50 cells/mm³)</td>
<td>Avoid overlapping side effects</td>
</tr>
<tr>
<td></td>
<td>Avoid PK interactions</td>
</tr>
<tr>
<td></td>
<td>Lower pill burden</td>
</tr>
<tr>
<td></td>
<td>Lower risk of IRIS</td>
</tr>
<tr>
<td><strong>CONS</strong></td>
<td><strong>CONS</strong></td>
</tr>
<tr>
<td>Overlapping side effects</td>
<td>Higher risk of HIV disease progression or death in advanced patients (CD4 &lt; 50 cells/mm³)</td>
</tr>
<tr>
<td>PK interactions</td>
<td></td>
</tr>
<tr>
<td>Higher pill burden</td>
<td></td>
</tr>
<tr>
<td>Risk of immune reconstitution disease</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from *J Acquir Immune Defic Syndr* 2007; 46: S9-S18.
- cohorte constituted in 2000 (data collected since 1984)
- « simultaneous »: HAART within 2 months after onset of TB Rx
- « nonsimultaneous »: HAART after 3 months of TB diagnosis
- Patients receiving HAART for more than 2 months before TB diagnosis excluded

Velasco M et al., J Acquir Immune Defic Syndr 2009
WHEN TO START HAART?

Several ongoing clinical trials

- PART Study in Uganda,

- TB-HAART in Uganda, Zambia, SA, Tanzania

  including the large studies:

- SAPIT in South Africa with interim data on mortality rates indicating a 55% reduction of mortality in the integrated TB-HIV arm

- AACTG A5221 Study (NIAID, US)

- CAMELIA (Joint ANRS, France & NIH-CIPRA, US) Study in Cambodia

Data expected within the next 2-4 years
# SUMMARY of ONGOING STRATEGY CLINICAL TRIALS

<table>
<thead>
<tr>
<th>Trial</th>
<th>Sponsor(s)</th>
<th>Country or countries (sample size)</th>
<th>Culture-confirmed TB at entry</th>
<th>CD4 cell count at entry, cells/mm²</th>
<th>TB treatment regimen</th>
<th>HAART regimen</th>
<th>Arms</th>
<th>Duration, months</th>
<th>Primary outcome(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAMELIA</td>
<td>ANRS (France) and NIAID/CIPRA (US)</td>
<td>Cambodia (N = 6601)</td>
<td>Mandatory</td>
<td>&lt;200</td>
<td>Standard 2EHRZ/4HR</td>
<td>d4T/3TC (generic) + EFV</td>
<td>Early: HAART 2 weeks after initiation of TB treatment. Late: HAART 8 weeks after initiation of TB treatment.</td>
<td>12</td>
<td>Survival</td>
</tr>
<tr>
<td>AACTG A5221b</td>
<td>NIAID (USI)</td>
<td>Brazil, Haiti, India, Malawi, Peru, South Africa, Thailand, Zimbabwe (N = 800)</td>
<td>Not mandatory</td>
<td>&lt;200</td>
<td>RIF- or RIB-based regimen</td>
<td>TDF/FTC (Truvada; Gilead) + EFV</td>
<td>Early: HAART within 2 weeks after initiating TB treatment. Late: HAART 6 to 12 weeks after initiating TB treatment.</td>
<td>12</td>
<td>Survival without AIDS progression</td>
</tr>
<tr>
<td>SAPIT</td>
<td>NIAID (USI)</td>
<td>South Africa (N = 592)</td>
<td>Not mandatory</td>
<td>&gt;60</td>
<td>Standard 2EHRZ/4HR</td>
<td>ddI/3TC + EFV</td>
<td>Integrated: HAART concurrent with standard TB treatment through DOT. Sequential: after completion of TB treatment, HAART without DOT.</td>
<td>18</td>
<td>Diagnosis of an AIDS-defining illness; mortality at 18 months</td>
</tr>
<tr>
<td>TB-HAARTf</td>
<td>WHO/TDR</td>
<td>South Africa, Tanzania, Uganda, Zambia (N = 1900)</td>
<td>Mandatory</td>
<td>&gt;200</td>
<td>Standard 2EHRZ/4HR</td>
<td>ZDV/GTC (Combivir; GlaxoSmithKline) + EFV or placebo</td>
<td>1: HAART initiated 2 weeks after initiation of TB treatment, concomitant with TB treatment until 6 months, then continuation with ART alone. 2: HAART placebo initiated 2 weeks after initiation of TB treatment, concomitant with TB treatment until 6 months, then HAART initiated.</td>
<td>24</td>
<td>Composite end point of TB treatment failure or death at 6 months after initiation of TB treatment</td>
</tr>
<tr>
<td>PARTg</td>
<td>NIAID (USI) and Makerere University (Uganda)</td>
<td>Uganda (N = 250)</td>
<td>Not mandatory</td>
<td>≥350</td>
<td>Standard 2EHRZ/4HR</td>
<td>ZDV/GTC/ABV (Trizivir; GlaxoSmithKline)</td>
<td>1: Initial HAART. 2: Delay HAART until CD4 cell count decreases to &lt;200 cells/mm².</td>
<td>24</td>
<td>CD4 cell count decrease (slope); time to AIDS</td>
</tr>
<tr>
<td>BKVIRb</td>
<td>ANRS (France)</td>
<td>France</td>
<td>Mandatory</td>
<td>...</td>
<td>Standard 2EHRZ/4HR</td>
<td>TDF/FTC (Truvada) + EFV</td>
<td>NA</td>
<td>12</td>
<td>Treatment success rate; plasma HIV-1 RNA level &lt;50 copies/mL; TB cured</td>
</tr>
</tbody>
</table>

**NEEDS FOR MORE CLINICAL TRIALS...**

**NEEDS FOR NEW TREATMENTS INCLUDING ANTI-TB DRUGS....**
Need to better understand the HIV-M. tuberculosis interplay in a common target, the macrophages...

Control of Bacteria Replication: Central role of Th1, IFNγ response.
NEED TO BETTER UNDERSTAND IRIS PATHOPHYSIOLOGY

- Immune restoration on HAART => *Immune reconstitution inflammatory syndrome (IRIS)/ Paradoxical reaction (PR)*

- IRIS frequency in HIV/TB ranging from 11% to 43%.

- Currently there are no laboratory test or accepted biological criteria for the diagnosis of IRIS.

- Mechanism of IRIS/PR remains to be clarified

- Understanding these mechanisms will help to identify the new predictive markers of IRIS/PR and consequently to improve IRIS diagnosis and patient care and treatment.

*Lancet Infect Dis 2008; 8: 516–23*
NEED TO BETTER UNDERSTAND THE MECHANISMS RESPONSABLE FOR IRIS

A question of balance between pro-inflammatory and anti-inflammatory responses

Role of innate and adaptive immunity?

New predictive makers to improve patient care?

PREVENTION OF IRIS
NEED TO IMPROVE TB PREVENTIVE INTERVENTIONS....

➢ Isoniazid preventive therapy to increase survival on HAART

Isoniazid preventive therapy, HAART and tuberculosis risk in HIV-infected adults in South Africa: a prospective cohort

Jonathan E. Golub\textsuperscript{a,b}, Paul Pronyk\textsuperscript{c,d}, Lerato Mohapi\textsuperscript{e}, Nketo Thsabangu\textsuperscript{e}, Mosa Moshabela\textsuperscript{d}, Helen Struthers\textsuperscript{e}, Glenda E. Gray\textsuperscript{e}, James A. McIntyre\textsuperscript{e}, Richard E. Chaisson\textsuperscript{a,b} and Neil A. Martinson\textsuperscript{a,e}

\textit{AIDS} 2009, 23:631–636

➢ TEMPRANO (ANRS 12136) Study: Ongoing Clinical randomized clinical trial in Ivory Coast (INH before HAART vs simultaneous INH and early HAART)

➢ New Mtb Vaccines ??.....
<table>
<thead>
<tr>
<th>Candidate -vaccines</th>
<th>Clinical Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>AERAS-rBCG</td>
<td>Phase I starting in 2009 in US</td>
</tr>
<tr>
<td>GSK M72</td>
<td>Phase I completed in Belgium Phase II started in 2008 in South Africa</td>
</tr>
<tr>
<td>SSI HyVac4 (AERAS-404)</td>
<td>Phase I clinical trial — Finland Phase I clinical trial — South Africa Phase I clinical trial — Sweden</td>
</tr>
<tr>
<td>rBCG-UreC-Hly MP-VPM/BPR</td>
<td>Planned</td>
</tr>
<tr>
<td>Mtb- PhoP HBHA UNIZAR/INSERM/ULB</td>
<td>Pre-exploratory meetings</td>
</tr>
</tbody>
</table>

**TB vaccine candidates: Ongoing trials…**

<table>
<thead>
<tr>
<th>Candidate -vaccines</th>
<th>Clinical Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>AERAS-rBCG</td>
<td>Phase I starting in 2009 in US</td>
</tr>
<tr>
<td>GSK M72</td>
<td>Phase I completed in Belgium Phase II started in 2008 in South Africa</td>
</tr>
<tr>
<td>SSI HyVac4 (AERAS-404)</td>
<td>Phase I clinical trial — Finland Phase I clinical trial — South Africa Phase I clinical trial — Sweden</td>
</tr>
<tr>
<td>rBCG-UreC-Hly MP-VPM/BPR</td>
<td>Planned</td>
</tr>
<tr>
<td>Mtb- PhoP HBHA UNIZAR/INSERM/ULB</td>
<td>Pre-exploratory meetings</td>
</tr>
</tbody>
</table>

**A very long term issue, far to be a solution for HIV…**
TB VACCINE RESEARCH: A challenging issue with similarities with HIV Vaccine Research…

- Mtb diversity
- Correlates of protection?
- Potential adverse effects?

- Need to understand why a vast majority of Mtb infected individuals are asymptomatic…
- Need to further dissect the immune response against Mtb and the pathogen response to immunization

Mtb and HIV vaccine researchers can probably learn from each other….

What is the right balance in favor of the host?
Further challenges in TB-HIV Research??

Need to improve

- the balance between basic vs translational research
- the interface between basic and clinical research
- the integration of research within other global intervention