*Catalysing HIV/TB research: innovation, funding and networking.*
*July 19, 2009.*
*University of Cape Town Medical School, Cape Town, South Africa.*

# CHALLENGES ON TUBERCULOSIS AND HIV RESEARCH.

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# TB-HIV COINFECTION: ALARMING INCREASE

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.

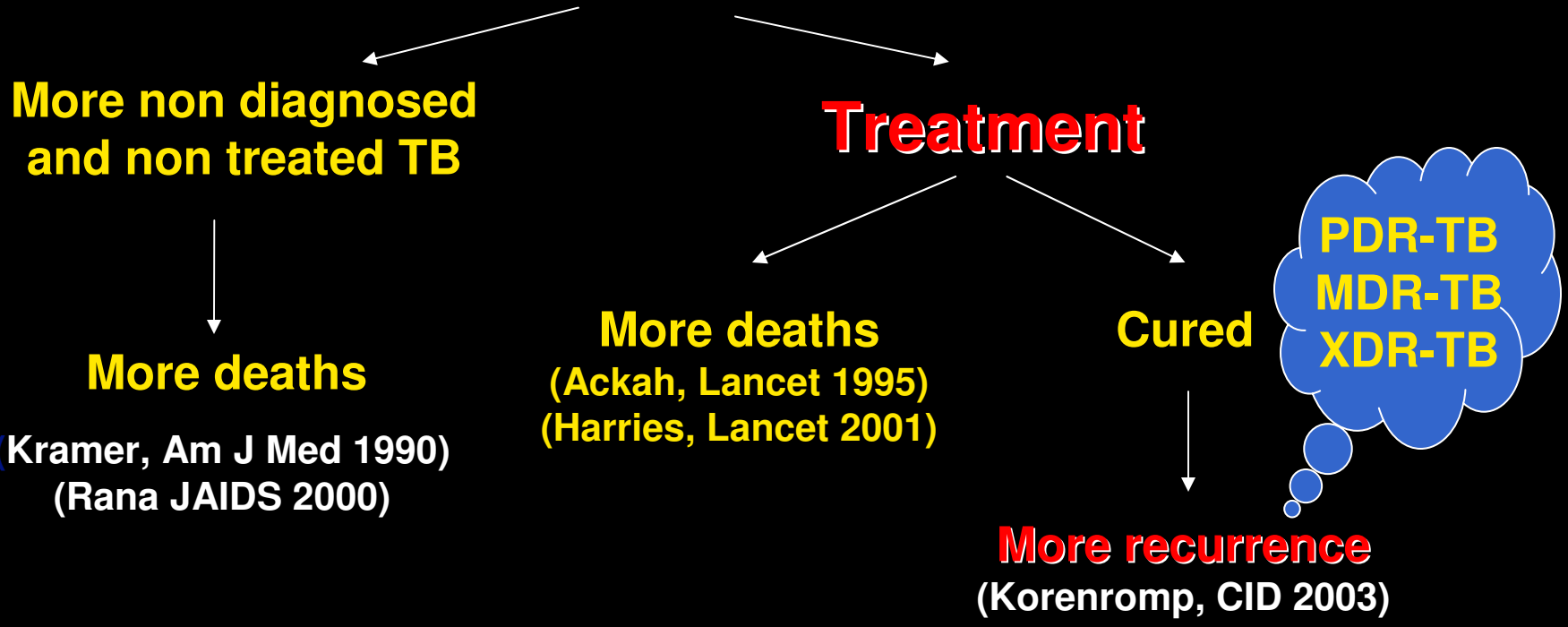
South Africa alone: accounts for over one quarter of all cases .

*Lawn, Churchyard. Curr Opin HIV AIDS 2009; 4(4): 325-33.*

# TB IS THE MOST COMMON ILLNESS AMONG HIV-INFECTED ADULT PATIENTS

Increased frequency of:

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




**20% of PLWH on HAART died of TB…**

# TB IN HIV-INFECTED PATIENTS

## 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

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

## Future

- 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:

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

Basirudeen Syed Ahamed Kabeer[1], Rajasekaran Sikhamani[5], Sowmya Swaminathan[2], Venkatesan Perumal[3], Paulkumaran Paramasivam[4], Alamelu Raja[1]*

*PLoS ONE, May 2009, Vol.4, Issue 5*

**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**

Review by T.Mori in

J Infect Chemother (2009) 15:143–155
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.**

# Challenges for TB Diagnosis in HIV+ Children

- **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 ?

| START TB TREATMENT AND HAART SIMULTANEOUSLY | START TB TREATMENT FIRST AND DELAY HAART |
|---|---|
| **PROS** | **PROS** |
| Lower risk of HIV disease progression or death in advanced patients (CD4 < 50 cells/$mm^3$ ) | Avoid overlapping side effects<br>Avoid PK interactions<br>Lower pill burden<br>Lower risk of IRIS |
| **CONS** | **CONS** |
| Overlapping side effects<br>PK interactions<br>Higher pill burden<br>Risk of immune reconstitution disease | Higher risk of HIV disease progression or death in advanced patients (CD4 < 50 cells/$mm^3$ ) |

Adapted from *J Acquir Immune Defic Syndr* 2007; 46: S9-S18.

# COMESEM cohorte, Madrid, Spain

- cohorte constituted in 2000 (data collected since 1984)
- TB diagnosis between 1987-2004: 1 217, incl. 322 after 1996
- « 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

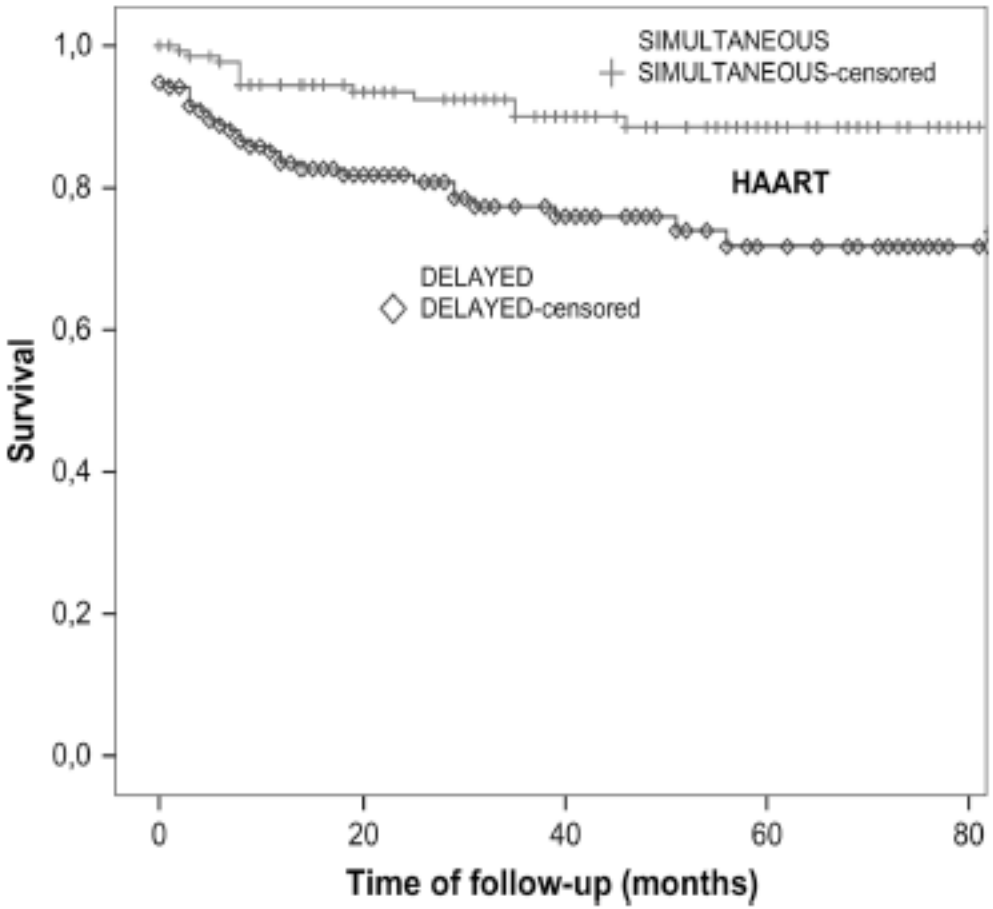



**FIGURE 1.** Survival evolution of HIV patients who started HAART and TB treatment at the same time (simultaneous) or after ≥3 months (delayed). Follow-up after the diagnosis of TB. Log-rank (Mantel–Cox) $P = 0.003$.

Velasco M et al., *J Acquir Immune Defic Syndr* 2009

# WHEN TO START HAART ?

***Several ongoing clinical trials***

-PART Study in Ugunda,

-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

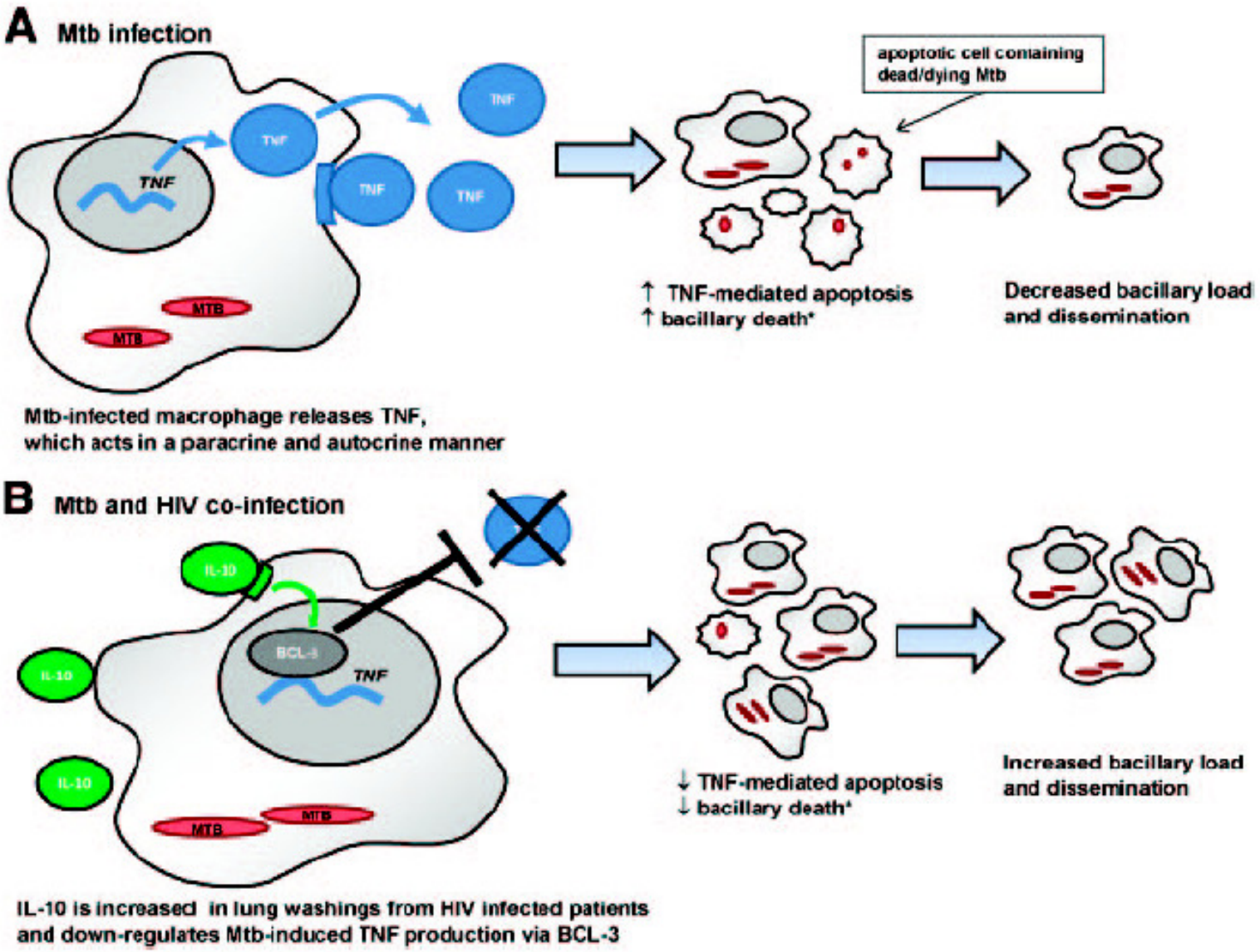
| Trial | Sponsor(s) | Country or countries (sample size) | Culture-confirmed TB at entry | CD4 cell count at entry, cells/mm$^3$ | TB treatment regimen | HAART regimen | Arms | Duration, months | Primary outcome(s) |
|---|---|---|---|---|---|---|---|---|---|
| CAMELIA[a] | ANRS (France) and NIAID/ CIPRA (US) | Cambodia (*N* = 660) | Mandatory | <200 | Standard 2EHRZ/4HR | d4T/3TC (generic) + EFV | Early: HAART 2 weeks after initiation of TB treatment. Late: HAART 8 weeks after initiation of TB treatment. | 12 | Survival |
| AACTG A5221[b] | NIAID (US) | Brazil, Haiti, India, Malawi, Peru, South Africa, Thailand, Zimbabwe (*N* = 800) | Not mandatory[c] | <200 | RIF- or RIB-based regimen | TDF/FTC (Truvada; Gilead) + EFV | Early: HAART within 2 weeks after initiating TB treatment. Late: HAART 8 to 12 weeks after initiating TB treatment. | 12 | Survival without AIDS progression |
| SAPIT | NIAID (US) | South Africa (*N* = 592) | Not mandatory[c] | >50 | Standard 2EHRZ/4HR | ddI/3TC + EFV | Integrated: HAART concurrent with standard TB treatment through DOT. Sequential: after completion of TB treatment, HAART without DOT. | 18 | Diagnosis of an AIDS-defining illness; mortality at 18 months |
| TB-HAART[f] | WHO/TDR | South Africa, Tanzania, Uganda, Zambia (*N* = 1900) | Mandatory | >200 | Standard 2EHRZ/4HR | ZDV/3TC (Combivir; GlaxoSmithKline) + EFV or placebo | 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. | 24 | Composite end point of TB treatment failure or death at 6 months after initiation of TB treatment |
| PART[g] | NIAID (US) and Makerere University (Uganda) | Uganda | Not mandatory[c] | ≥350 | Standard 2EHRZ/4HR | ZDV/3TC/ABV (Trizivir; GlaxoSmithKline) | 1: Initial HAART. 2: Delay HAART until CD4 cell count decreases to <200 cells/mm$^3$. | 24 | CD4 cell count decrease (slope); time to AIDS |
| BKVIR[h] | ANRS (France) | France | Mandatory | … | Standard 2EHRZ/4HR | TDF/FTC (Truvada) + EFV | NA | 12 | Treatment success rate; plasma HIV-1 RNA level <50 copies/mL; TB cured |

The Journal of Infectious Diseases 2007;196:S46–51

**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, IFN□.□□□respo nse..

Volume 86, July 2009 *Journal of Leukocyte Biology*

# 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

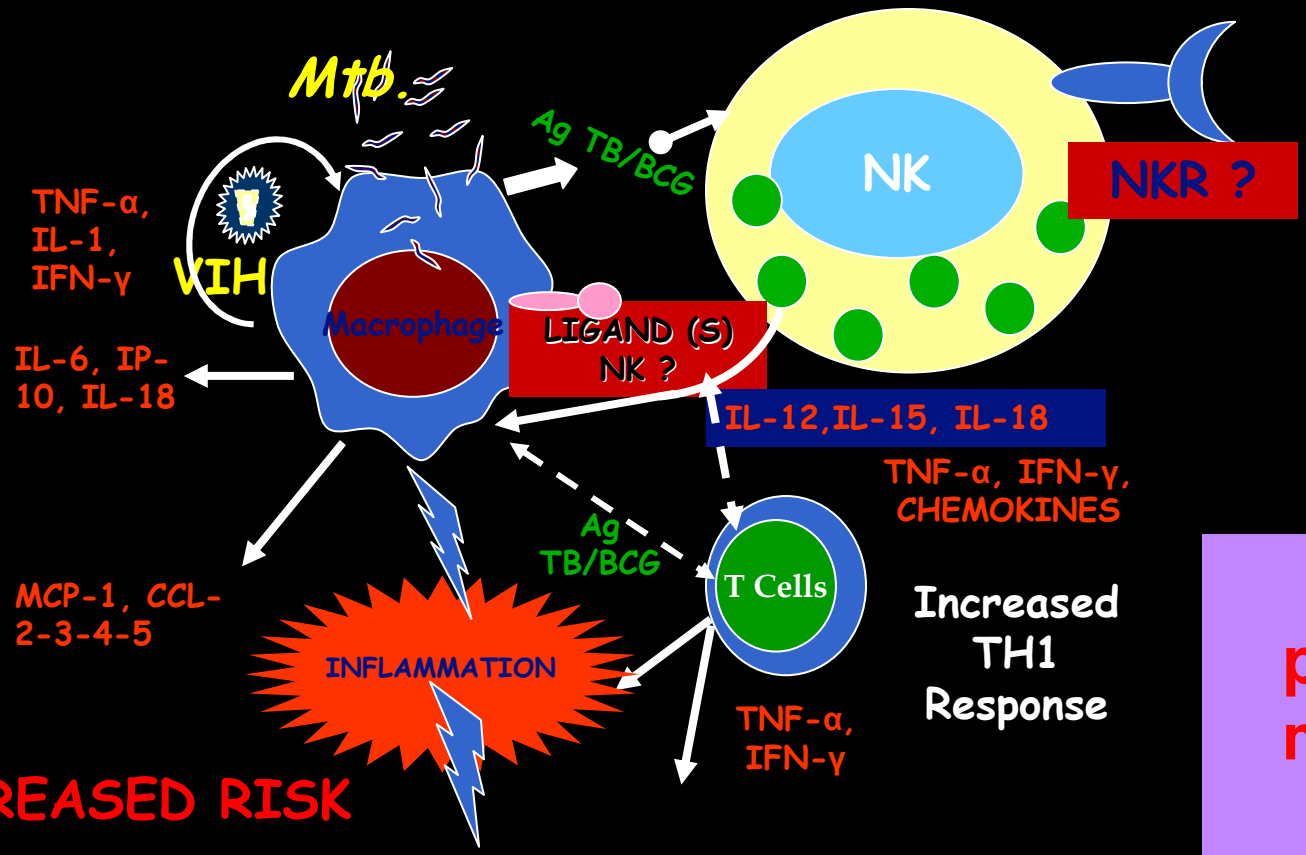
- Understanding these mechanisms will help to identify the new predictive markers of IRIS/PR and consequently to improve IRIS diagnosis and patient care and treatment.

*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?




INCREASED RISK OF IRIS

CAPRI-NK& T -ANRS study

**New predictive makers to improve patient care?**

# 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[a,b], Paul Pronyk[c,d], Lerato Mohapi[e], Nkeko Thsabangu[e], Mosa Moshabela[d], Helen Struthers[e], Glenda E. Gray[e], James A. McIntyre[e], Richard E. Chaisson[a,b] and Neil A. Martinson[a,e]

*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 ??…..**

# TB vaccine candidates: Ongoing trials…

| Candidate -vaccines | | Clinical Trials |
|---|---|---|
| **AERAS-rBCG** | recombinant BCG overexpressing selected antigens and endosome escape to enhance antigen immunogenicity | Phase I starting in 2009 in US |
| **AERAS-402/Crucell Ad35** | replication-deficient adenovirus contains M. tuberculosis antigens 85A, 85B, and TB10.4 and induces high levels of CD8+ T cell responses, | Phase I completed in US (2006) Phase I in progress in South Africa and Kenya. A Phase II in adults exposed to TB in progress in South Africa. |
| **MVA85A/Aeras-485** | modified vaccinia virus Ankara (MVA) as vaccine delivery system | Phase I in the UK, The Gambia, and South Africa and Phase II trials in South Africa and The Gambia completed. Phase IIb — proof of concept — started april 2009 in, South Africa. |
| **GSK M72** | immunogenic fusion recombining two proteins + GSK adjuvants | Phase I completed in Belgium<br>Phase II started in 2008 in South Africa |
| **SSI HyVac4 (AERAS-404)** | fusion protein using SSI's HyVac4 (H4) antigen (a fusion protein of 85B and TB10.4), combined with Intercell's<br><br>IC31 adjuvant to stimulate T cell-mediated immunity. | Phase I clinical trial — Finland<br>Phase I clinical trial — South Africa<br>Phase I clinical trial — Sweden |
| **rBCG-UreC-Hly MP-VPM/BPR** | Modified version of BCG with protein listeriolysin O (Hly) and deficient in urease C | Planned |
| **Mtb- PhoP HBHA UNIZAR/ INSERM/ULB** | PhoP deletion mutant of M.Tuberculosis + methylated HBAHA antigen in adjuvant | Pre-exploratory meetings |

**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**

**What is the right balance in favor of the host?**

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

# 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

International AIDS Society
Stronger Together

**THANKS FOR YOUR ATTENTION !**