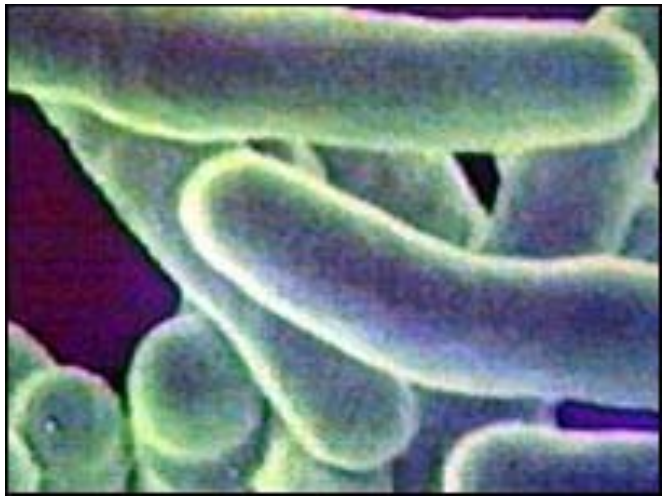
Contribution of genetic variation to pharmacokinetic variability and toxicity in patients undergoing multi-drug tuberculosis treatment in Sub-Saharan Africa: RAFAgene project



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Background

Tuberculosis (TB):

- Important cause of death in Sub-Saharan Africa
- In best-case of TB treatment scenario, **≈ 10% of patients cannot be cured**
- Complex relationship between TB pathogen, drugs and host
- Genetic variability of the host might play an important role for treatment response

General Aim

- **To conduct :**
  - **a pharmacogenetic study**
  - **of TB drugs** (Rifampicin, Isoniazid, Ethambutol, Pyrazinamide and Gatifloxacin)
  - **in TB patients in Sub-Saharan Africa**

Specific aims

1. To assess the **role of host genetic variation on the pharmacokinetics (PK)** of TB drugs
2. To assess the role of **genetic variation in host** genes governing PK **on:**
   a. **the efficacy** of TB treatment
   b. **the safety** of TB treatment
3. To validate **functional mechanisms** for putative associations.

RAFAgene partners

University of Liverpool (UK)

(Genetic analysis)

London School of Hygiene & Tropical Medicine (UK)

(Genetic epidemiology)

National TB program (Dakar), **study site**

National TB program (Conakry) **study site**

National Hospital for TB and Pulmonary Diseases(Cotonou, Benin) **study site**

MRC SA (Durban,, **study site**

Cape Town University

(PK/ PD)

Study design and population (1)

Study participants from 2 clinical trials:

- *OFLOTUB trial (completed)*
- *RAFA trial (ongoing)*

Study design and population (2)

OFLOTUB: To shorten TB Treatment

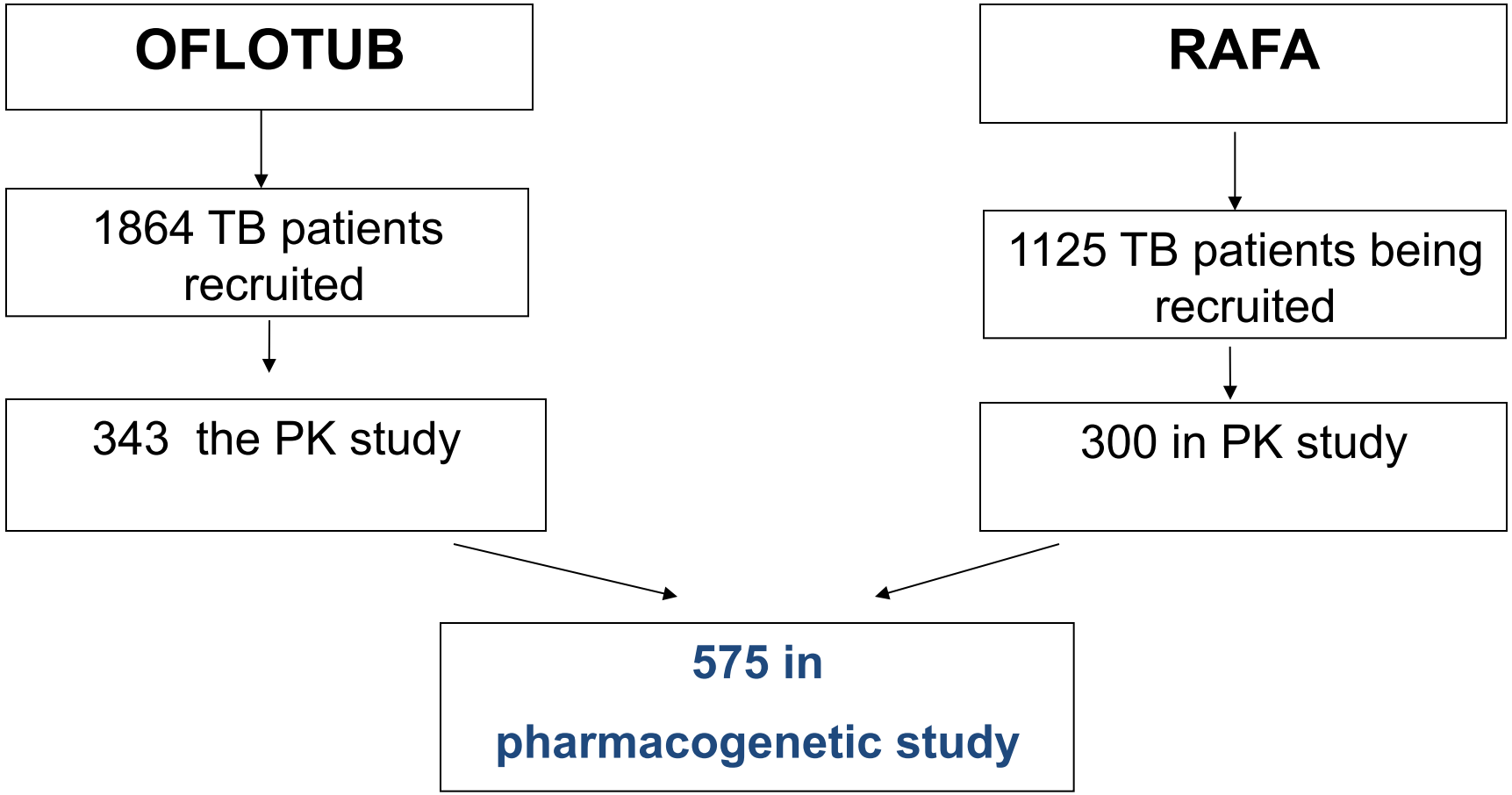
Arm	Intensive phase	Continuation phase	Particularity
1	2ERHZ	4RH	6 months
2	2GRHZ	2GRH	4 months

Study design and population (3)

RAFA: To improve TB/ HIV co-infected treatment

Arm	Intensive phase	Continuation phase	Particularity
1	2ERHZ	4RH	ART at15 days
2	2ERHZ	4RH	ART at 2 months
3	2ERHZ	4RH	ART at 2 months + High R

Study design and population (4)



Pharmacokinetic (PK) analysis

- Serial blood samples(pre-dose and at various hours after TB treatment dosing)
- Samples processed and analyzed by liquid chromatograph mass-spectrometry (LC-MS)
- Area under the curve (AUC) measured

PK/PD outcome measures

PK outcome measures: AUC for TB drugs

PK/ PD outcome measures:

Primary Outcome measure: Unfavorable TB treatment outcome (failure / recurrence / death)

Secondary outcome measures:

- Relapse 1 year after the end of the TB treatment
- Treatment failure
- Time to TB culture conversion
- Type, frequency and severity of Adverse Drug reaction

Genetic analysis

Comprehensive approach to identify relevant genetic markers relevant to drug absorption, distribution, metabolism, and elimination (ADME):

- **Affymetrix** DMET Plus Premier Pack comprising 1936 polymorphisms in ~230 genes relevant to ADME
- **Sequenom** iPlex platform or **real-time PCR** for a number of hypothesis-driven targeted variants in genes not covered in Affymetrix (based on litterature).

Functional validation

If association PK/PD and genetic analysis, **mechanistic relevance of single nucleotide polymorphisms (SNPs)** will be evaluated:

- To confirm the biological plausibility
- To help understand underlying mechanisms of identified SNP associations

A range of in vitro techniques will be employed

Capacity building (1)

Senegal, Guinea: Good Laboratory Practices training
Benin: DNA archive establishment **Benin:** Implementation in Benin of **real time PCR** for genetic analysis to facilitate future genetic research studies.

Capacity building (2)

Capacity strengthening proposed
Building of a larger team with: - Expertise in (pharmaco) genetics, epidemiology, statistical genetics and bioinformatics - A hub in Benin through training of younger African scientists: **1 PhD, 2 MSc and various courses (PK, TESA courses, genetic epidemiology)** Participation in international research meetings

Where are we?

- **Oflotub trial:**
  - Completed
  - PK/PD data available
- **Rafagene project:**
  - On-going
  - 160/ 300 already in PK study

Where are we?

- **Protocol:**
  - Draft available, input from NIH
  - Being circulated among partners for finalization
- **Informed consent:**
  - Draft available, being circulated
  - To be improved with aspects discussed during this meeting

Problems faced

- Delay in getting the funds leading to a delay in getting full involvement of all partners

- **Already fixed**

Perspectives

- Help offered by NIH:
  - Financial aspects
  - Administrative issues
  - Technical aspects

Next steps

- Finalization of the protocol/ translation in french
- Ethical clairance
- While waiting for ethical clairance:
  - Training for dedicated staff
  - Development of all SOPs
  - Ordering consumables/ reagents

Thank you