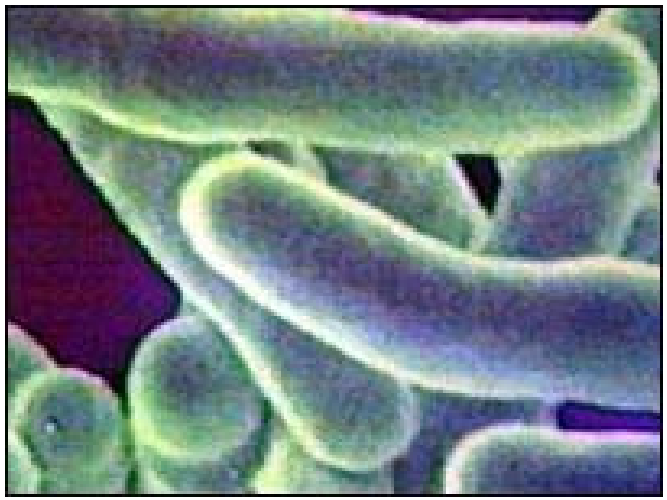
Contribution of genetic variation to pharmacokinetic variability and toxicity in patients undergoing multi-drug tuberculosis treatment in Sub-Saharan Africa**:**

RAFAgene project



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RAFAgene

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

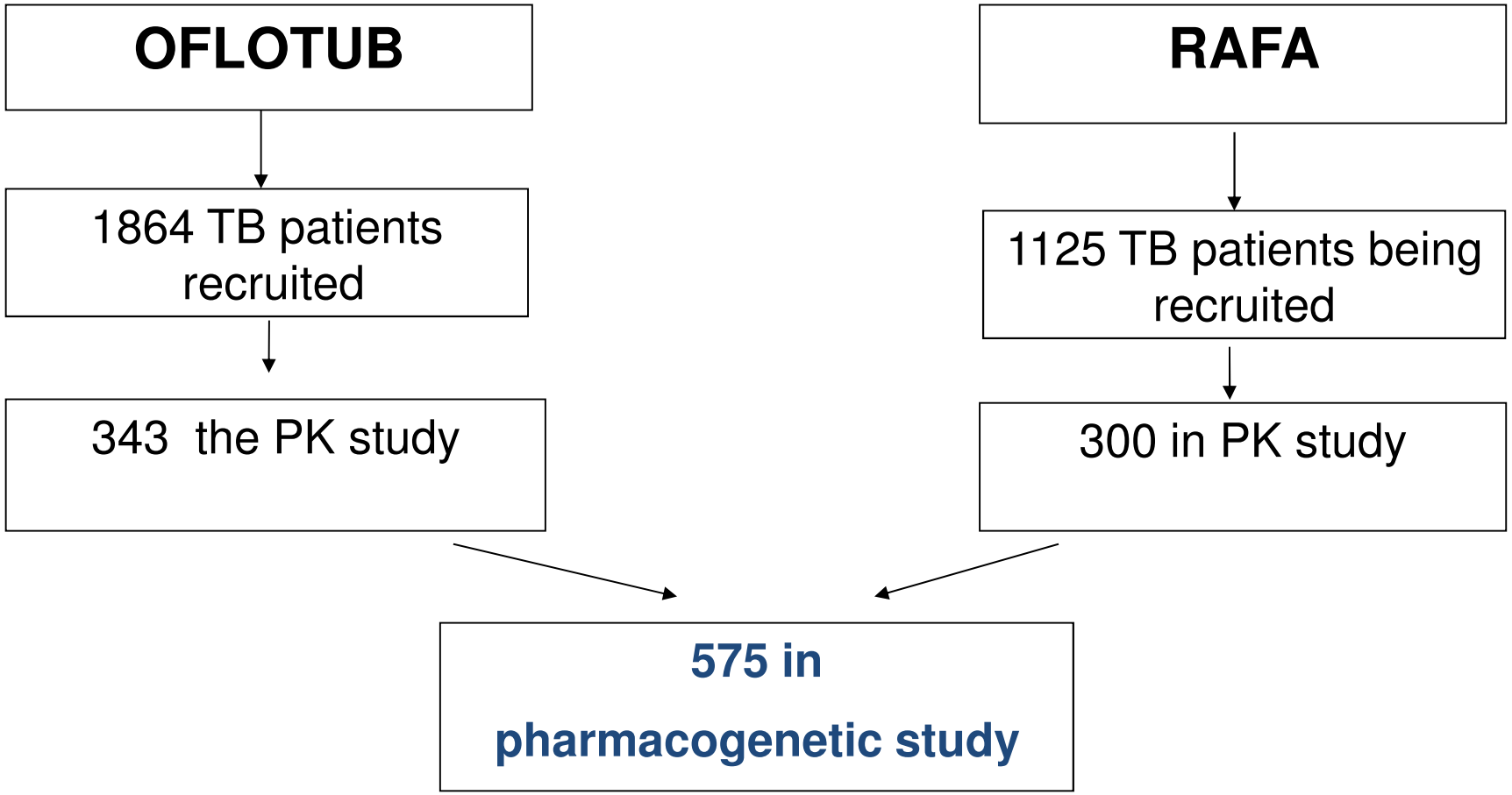
Arm	Intensive phase	Continuation phase	Particularity
1	2ERHZ	4RH	6 months
2	2GRHZ	2GRH	4 months

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

- **Done in primary studies (Oflotub and Rafa)**
  - 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

- **Done in primary studies (Oflotub and Rafa)**

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, treatment failure, time to TB culture conversion, type, frequency and severity of Adverse Drug reaction

Genetic analysis (in Rafagene)

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 (343 subjects)
  - PK/PD data available
- **Rafagene project:**
  - On-going
  - **200**/ 300 already in PK study

Where are we?

- **Protocol/ informed consent finalized**
- **Study sites assessed**
- **540 subjects already recruited** in primary studies (total to be recruited = **575**)
- **Masters/ PhD students appointed**

Next steps

- While waiting for ethical clairance:
  - Training for dedicated staff
  - Development of all SOPs
  - Ordering consumables/ reagents
- Patients recruitment (1 – 2 months)
- Lab analysis
- Data analysis

Thank you