Safety tolerability and monitoring of combined anti-tuberculosis and antiretroviral therapy.

A substudy to:

"Bioavailability of the fixed dose formulation Rifafour containing isoniazid, rifampicin pyrazinamide, Ethambutol and the WHO recommended first line anti-retroviral drugs zidovudin, lamivudine, efavirenz administered to new TB patients at different levels of immunosuppression".

Thuli Mthiyane

South African Medical Research Council
BUILDING A HEALTHY NATION THROUGH RESEARCH

6-Arm pharmacokinetic study

- Investigates the bioavailability of rifampicin, isoniazid, zidovudine, lamivudine and efavirenz administered as follows:

  - **TB/HIV co-infected (220-349 CD4 T cells/µl) treated with anti-TB chemotherapy + HAART**
  - **TB/HIV co-infected (220-349 CD4 T cells/µl) treated with anti-TB chemotherapy**
  - **TB/HIV co-infected (350-500 CD4 T cells/µl) treated with anti-TB chemotherapy + HAART**
  - **TB/HIV co-infected (350-500 CD4 T cells/µl) treated with anti-TB chemotherapy**
  - **TB/ HIV co-infected (<200 CD4 T cells/µl) receiving anti-TB chemotherapy + HAART**
  - **HIV infected without active TB (<200 CD4 T cells/µl) receiving HAART**

Study design

	Group 1 HIV-TB	Group 2 HIV-TB	Group 3 HIV (non- TB)
	Intervention	Intervention	Intervention
Stratum 1 **350-500 cells/μl**	**HAART +SCC**	**SCC ***	
Stratum 2 **220-349 cells/μl**	**HAART + SCC**	**SCC ***	
Stratum 3 **< 200 cells /μl**	**HAART + SCC**		**HAART**

Study Aim

The purpose of the study is to:

- **compare side effects including hepatotoxicity and immune reconstitution syndrome of participants receiving concomitant treatment for HIV and TB co infection with those receiving TB treatment alone.**
- **determine the effects of polymorphism in N-acetyltransferace and cytochrome P450 on toxicity and pharmacokinetics of combined TB and HIV therapy.**
- **determine the effect on Health Related Quality of Life (HRQOL) when ARVs are introduced early during TB treatment or after completion of treatment.**
- **investigate the utility of INF- γ release assay in the monitoring of immune reconstitution and outcome of therapy in patients treated with TB and HIV therapy.**

Study objectives and methods

Objective 1

To determine if there is a difference in the experience of

a. adverse events (AEs) and serious adverse events (SAEs)

b. hepatotoxicity grade 1-4 (case-control)

c. immune Reconstitution Syndrome

in TB/HIV co infected patients receiving TB treatment and HAART concomitantly and TB/HIV co infected patients receiving TB treatment then commencing HAART.

Objective 2

To determine if patients starting ARVs early during TB treatment have a better HRQOL than patients starting ARVs after completion of TB treatment in TB/HIV co infected patients.

Objective 3

To determine polymorphisms in cytochrome P450 and N-acetyltransferace and their relationship to hepatotoxicity and efavirenz bioavailability in participants receiving anti-TB treatment and HAART.

Objective 4

To determine the kinetics of mycobacterial cellular immune responses in patients treated with HAART and tuberculosis drugs using an INF- γ release assay.

Study progress

- **59 patients have been recruited**
- **Samples collected and processed in batches for HepB & C and INF-y**
- **Samples collected for batch processing for Cytochrome P450 and NAT2**

Challenges

- Recruitment of patients in higher CD4 count groups
- Changes in CD4 counts within period of treatment

Responses to challenges

- **Spread out to other clinics to increase recruitment**
  - **More staff needed for additional sites**

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MRC
The study team involved include:

- Country PI R Rustomjee
- 1 Clinician L Gabela
- 1 HIV Specialist & supervisor A Pym
- Pharmacist: B Harilal and S Rambaran
- 4 Clinical trial Nurses T Buthelezi, A Nyembe and Z Ngcobo
- 3 counsellors T Zulu, T Mthembu, and N Saul
- 2 counsellor drivers M Dladla and F Dube

WHO/TDR

- Study Director P Onyebujoh
- M Gomes
- Country coordinator F Baiden
- Study monitor J Fernandes