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Determining the optimal doses of antiretroviral and anti-tuberculous medications when used in combination for the treatment of HIV/TB in co-infected patients

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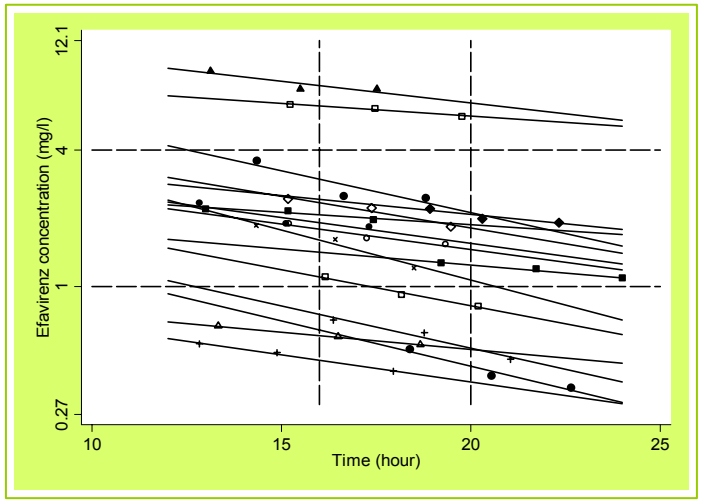
Objectives

- Describe and compare ARV (LPV, EFV, NVP) concentrations, in HIV-infected CHILDREN and ADULTS, with and without RIFAMPICIN-based TB treatment.
- Identify risk factors in African populations for low of high ARV concentrations

- Association of efficacy and safety with concentrations of the ARVs
- Rifampicin and isoniazid concentrations
- WB, plasma, intracellular, free drug concentrations
- Genetic polymorphisms
- Sample collection methods suitable for ARV concentration monitoring in resource-constrained settings
- Population pharmacokinetic (PK) and PK-PD models using NLME

Methods

- 5 studies:
  - EFV PK in children (standard doses)
  - LPV/RTV PK in children (double dose Kaletra® during TB treatment)
  - LPV/RTV PK in adults (1.5 x and 2 x dose Kaletra® once established on rifampicin)
  - NVP PK in children (standard dose, ? site)
  - NVP PK in adults (? site, ?design)
- Assay methods:
  - LC-MS/MS (accurate, ↓ volume samples)
  - Plasma, WB, intracellular, free
- Covariates:
  - Patient and treatment factors
- Analysis:
  - Trough concentrations, NCA, NLME
  - TB/HIV during- / after- TB treatment / controls / recommended ranges



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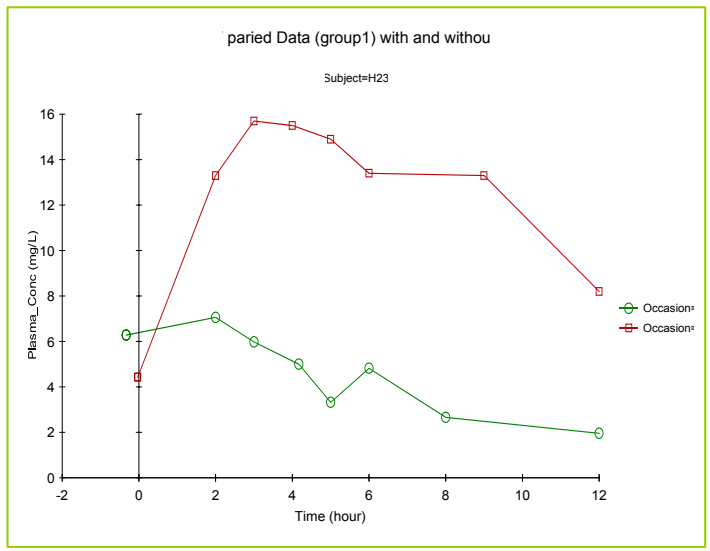
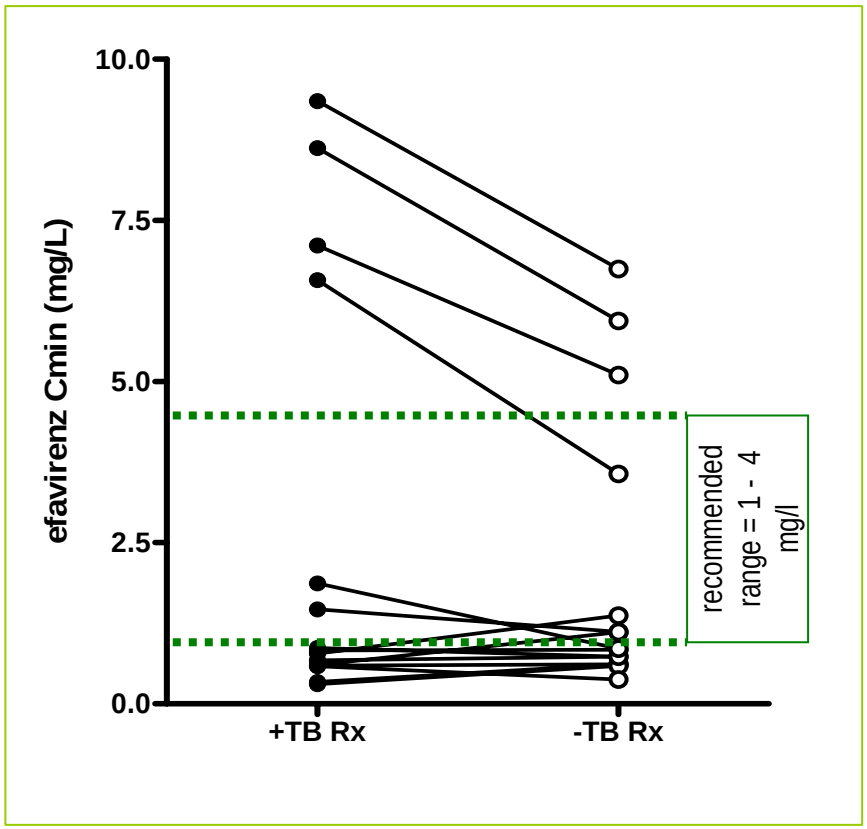


Results *(pilot studies in children)*

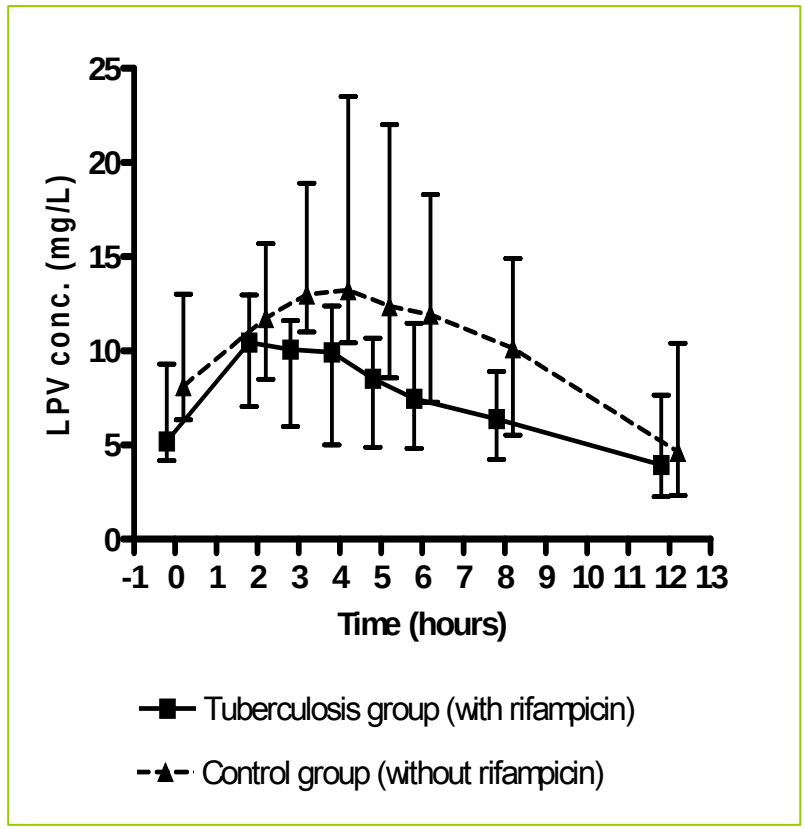
Trough [EFV] in 13 South African children receiving standard doses of EFV during and after TB treatment



Median Cmin: **0.83 mg/L (0.59-6.57)** **vs.** **0.86 mg/L (0.61 – 3.56)**

p=0.212 *(WSR test, paired data)*

LPV/RTV 1:1+2NRTIs in children with TB/HIV
vs.
LPV/rtv 4:1 (Kaletra®) in children without TB



Median Cmin: **3.94 mg/L (2.26, 7.66)** **vs.** **4.64 mg/L (2.32, 10.40)**

p=0.468 *(WSR test, independent data)*

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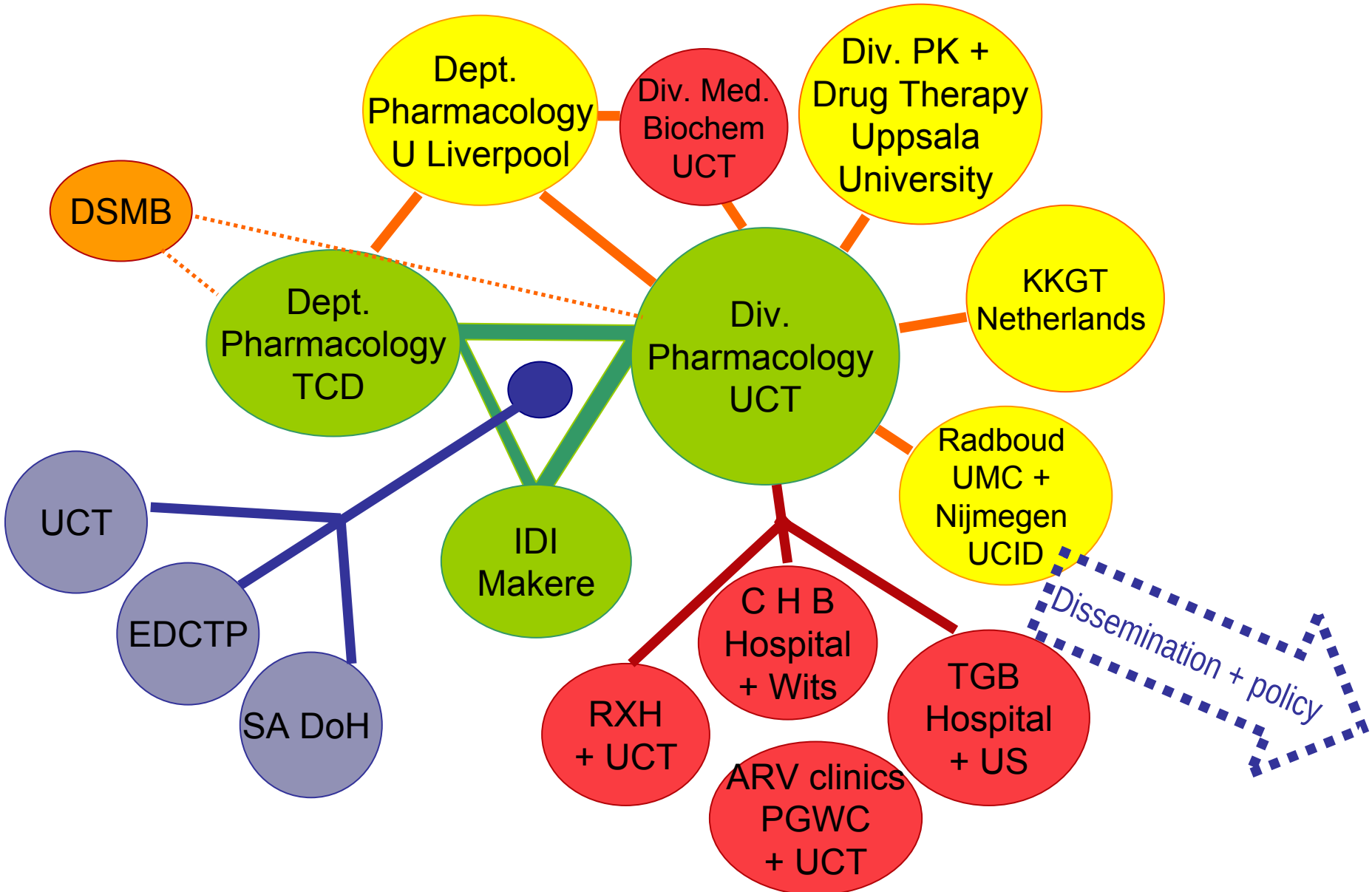
Capacity building

- PK study capacity at clinical sites
- GCP training and experience
- Assay methodology development
- Equipment: LC-MS/MS
- Technology transfer
  - NLME modeling
  - Assay methodology
- PhDs
  - scholarship in Kampala
  - students in Cape Town and Uppsala
- TDM service in Cape Town up and running

Networking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TGB Hospital + US
ARV clinics PGWC + UCT
Dissemination + policy

Conclusions

- Pilot studies have demonstrated the importance of PK evaluation in the relevant patient populations
- Ongoing studies
  - ↑ sample size
  - covariate effects, safety and efficacy
  - adjusted dosing approaches
  - WB concentrations
  - exploration of intracellular and free drug concentrations
- Challenges
  - changing environment of standard practices, treatment guidelines and available formulations
  - study population and design for optimizing NVP dose with TB treatment
  - translation of study findings into policy recommendations

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