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Cohort profile of a study on outcomes related to tuberculosis and antiretroviral drug concentrations in Uganda: design, methods and patient characteristics of the SOUTH study

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ABSTRACT

Purpose Tuberculosis (TB) is a leading cause of death among people living with HIV in sub-Saharan Africa. Several factors influence the efficacy of TB treatment by leading to suboptimal drug concentrations and subsequently affecting treatment outcome. The aim of this cohort is to determine the association between anti-TB drug concentrations and TB treatment outcomes.

Participants Patients diagnosed with new pulmonary TB at the integrated TB-HIV outpatient clinic in Kampala, Uganda, were enrolled into the study and started on first-line anti-TB treatment.

Findings to date Between April 2013 and April 2015, the cohort enrolled 268 patients coinfected with TB/HIV ; 57.8% are male with a median age of 34 years (IQR 29–40). The median time between the diagnosis of HIV and the diagnosis of TB is 2 months (IQR 0–22.5). The majority of the patients are antiretroviral therapy naive (75.4%). Our population is severely immunosuppressed with a median CD4 cell count at enrolment of 163 cells/µL (IQR 46–298). Ninety-nine per cent of the patients had a diagnosis of pulmonary TB confirmed by sputum microscopy, Xpert/RIF or culture and 203 (75.7%) have completed TB treatment with 5099 aliquots of blood collected for pharmacokinetic analysis.

Future plans This cohort provides a large database of well-characterised patients coinfected with TB/HIV which will facilitate the description of the association between serum drug concentrations and TB treatment outcomes as well as provide a research platform for future substudies including evaluation of virological outcomes.

Trial registration number NCT01782950; Pre-results.

Strengths and limitations of this study

- This is a prospective pharmacokinetic study with a relatively large sample size.
- Pharmacokinetic analysis performed at three time points and on three occasions enables us to estimate the maximum concentrations better.
- The main limitation of this study is that directly observed therapy is only performed on the study visit and not throughout the course of tuberculosis treatment.

INTRODUCTION

HIV infection is a major risk factor for the development of active tuberculosis (TB) and has been associated with poorer outcomes and higher relapse rates worldwide.[1]

The treatment of TB in patients coinfected with HIV poses several challenges and a number of factors potentially influence the efficacy of anti-TB drugs. These factors include side effects of treatment, significant drug–drug interactions with antiretroviral therapy (ART)[2] potentially leading to suboptimal drug concentrations[3] and comorbidities or opportunistic infections which can cause malabsorption. HIV infection, in addition to TB infection itself, might be a possible risk factor for poor absorption of anti-TB drugs.[4 5]

TB remains the leading cause of death among persons infected with HIV, especially in sub-Saharan Africa. While the vast majority of the patients coinfected with TB and HIV live in sub-Saharan Africa,[6] resources and technical capacity to measure drug concentrations in this region is limited, if not completely unavailable.

Several studies have demonstrated that patients with TB have suboptimal concentrations of anti-TB drugs in blood. Patients with TB/HIV coinfection are known to have poor drug absorption which contributes to the suboptimal concentrations. The consequence of this is still unclear. Data that characterise the pharmacokinetics of

first-line anti-TB drug concentrations in severely immunosuppressed patients with HIV and its association with treatment outcome and toxicities are still limited. Some studies demonstrating poor treatment outcomes and slow treatment response in patients with suboptimal pyrazinamide, rifampicin or isoniazid concentrations while other studies show no association between anti-TB drug concentrations and treatment outcomes.[7–9]

We established a clinical cohort of indiviuals coinfected with HIV/TB in order to contribute to the characterisation of the association between anti-TB drug concentrations over the entire anti-TB treatment period, TB treatment outcomes in this population. Our hypothesis is that patients coinfected with TB/HIV with suboptimal anti-TB drug concentrations have more unfavourable TB treatment outcomes compared with those with normal concentrations.

The aim of this paper is to describe the establishment of this well-characterised cohort of HIV-positive patients with confirmed pulmonary TB. In addition, we describe the scope and design of the cohort, as well as the profile of the enrolled patients.

COHORT DESCRIPTION

The participants of this cohort were enrolled at the Infectious Diseases Institute (IDI), Kampala, Uganda, a Makerere University centre of excellence in HIV care and treatment[10] with currently 8000 active patients, and 350–400 newly diagnosed TB cases seen annually.

In order to improve outcomes of HIV patients coinfected with TB in 2008, an integrated HIV-TB clinic was established[11]; patients diagnosed with TB are attended by a dedicated well-trained clinical team providing care for both HIV and TB and receive drugs from a separate pharmacy. Additional data with particular attention to TB care are entered in the IDI electronic medical record system.[12]

Study design and procedures

In this context, this study aims to describe the pharmacokinetic parameters of anti-TB drugs at different time-points over the course of treatment for pulmonary TB, and to investigate the association between serum concentrations of anti-TB drugs and TB treatment response in individuals coinfected with HIV/TB. The patients enrolled into the 'Study on Outcomes related to TB and HIV drug Concentrations in Uganda' (SOUTH) are followed up as a cohort for 5 years after the diagnosis of pulmonary TB. This cohort provides a research platform for substudies in order to answer diverse research questions.

Subjects were considered eligible for the study if they were willing to participate and to comply with the study procedures, if they were ≥18 years old, HIV infected and diagnosed with proven or highly suspected new pulmonary TB. Patients with extrapulmonary TB were excluded because treatment outcome assessed by clearance of mycobacteria from sputum by the end of treatment is our primary objectives and ascertainment of this would be challenging in patients with extrapulmonary TB. Patients were also excluded if they are pregnant or are planning a pregnancy, if they were part of an interventional study, had comorbidities that reduced life expectancy to less than a year (eg, disseminated Kaposi's sarcoma and other cancers), if they had evidence of decompensated liver disease and/or aminotransferases>5x upper limit of normal or a glomerular filtration rate (GFR) less than 50 mL/min. Patients are withdrawn from the study on patient request or based on medical judgement of the study doctor, if they became pregnant, develop a toxicity necessitating change or interruption of TB treatment, if the drug sensitivity test (DST) shows resistance to any first-line anti-TB drug, if they develop Immune Reconstitution Inflammatory Syndrome in organs other than the lungs (eg, tuberculous meningitis) or if their baseline culture identifies only mycobacteria other than *Mycobacteria tuberculosis*.

Sample size calculation: In previous studies which demonstrated that subtherapeutic pyrazinamide concentrations were associated with poor treatment outcome, subtherapeutic pyrazinamide concentrations were found in 33% of the study population.[13] In addition, prior data indicate that the failure rate for TB treatment is estimated to be 5%. We assumed that 33% of our study population will have subtherapeutic pyrazinamide concentrations and varied their TB treatment failure rate between 1% and 7%. Taking into account a 12.5% non-response rate, a sample size of 400 patients will be sufficient for us to reject the null hypothesis that the failure rates for patients with subtherapeutic concentrations and patients with normal concentrations are equal with a type I error probability of 0.05 and a power of 80%.

All consecutive patients with newly diagnosed pulmonary TB (proven or highly suspected) were screened over a period of 24 months and started on TB treatment at enrolment. First-line TB treatment was administered according to WHO guidelines,[14] consisting of rifampicin, isoniazid, pyrazinamide, ethambutol during the first 8 weeks (intensive phase), followed by rifampicin and isoniazid (continuation phase) for 16 weeks (a total of 24 weeks of TB treatment). Patients with positive sputum smears after 8 weeks of treatment received intensive phase treatment for an additional 4 weeks (up to week 12) with a total duration of 28 weeks of TB treatment. Patients were put on an efavirenz-based ART regimen if on first-line ART and lopinavir or atazanavir (both boosted with ritonavir)-based ART regimens if in need of second-line treatment. The ART initiation was scheduled at 2 weeks after initiation of TB treatment regardless of the CD4 count in ART-naive patients.

Enrolled patients are followed up for 6 months during TB treatment and undergo scheduled study visits at 2, 8 and 24 weeks of TB treatment or 28 weeks for those who were still sputum smear positive at week 8. After completing TB treatment, patients are followed up for a total of 5 years from enrolment to ascertain long-term clinical outcomes.

At every visit a comprehensive patient history focusing on evolution of cure and treatment-associated side effects is taken and meticulous physical examination is performed.

Anti-TB drug concentrations are measured at week 2, 8 and 24 or 28 at different time points after witnessed drug intake: 1 hour, 2 hours and 4 hours postdosing. Laboratory safety tests including a full blood count, liver and renal function tests are also performed on these study visits. Patients receive a light meal consisting of a boiled egg, 250 mL of milk, biscuits and a banana given after the 1 hour blood draw. The study physicians are blinded regarding drug concentrations until the end of the study or in case of treatment failure.

Sputum is collected for microscopy and cultures at the baseline visit, week 2, 8, and 24 or 28 where applicable. Patients who receive a prolonged intensive phase also have sputum analysis at week 12. DST is performed at baseline, week 8, 24 or 28 for sputum culture positive samples. Chest X-rays are performed at baseline, week 8 and week 24. In addition, biological samples (blood and sputum isolates) from the baseline visit, week 2, 8, 12 if applicable, and 24 or 28 are stored for future tests including pharmacokinetic analysis.

Safety laboratory tests, CD4 cell count and viral load measurements are performed at the Makerere University John Hopkins University (MUJHU) Core Laboratory, which is College of American Pathologists (CAP)-certified; TB sputum microscopy and culture at the Medical and Molecular Laboratories—Mycobacteriology Laboratory located in Mulago National referral Hospital which is also CAP-certified; Xpert MTB/RIF (Cepheid) tests and measurement of serum drug concentrations at the IDI research translational laboratory.

Data collection

Three different data collection tools are used for data collection: (1) At IDI comprehensive information is collected at enrolment in the programme and during follow-up for all patients, for example, social and demographic information, symptoms of TB and TB outcome and drug history. Data are entered in real time at each visit by providers into an electronic medical record system called Integrated Clinic Enterprise Application (ICEA), an in house built system based on *Microsoft.NET* technologies.[15] This system is used for the entire HIV outpatient clinic at IDI and ensures a high standard of data collection. (2) DataFax study case report forms (CRF) specially designed for the SOUTH study are used to collect study-specific information including time of drug and food intake, dose of drugs, information on adverse events and adherence information. DataFax is a data management system designated to manage paper data forms; when the faxed form reaches the DataFax server the system reads the data using intelligent character recognition and enters the data into the study database. In order to avoid double collection of data on the same visits, the DataFax CRF does not contain any information already collected into ICEA. (3) The drug concentrations are entered into an EpiData database by the laboratory technician to ensure blinding of providers.

Laboratory results performed in MUJHU Core Laboratory are entered into the laboratory database which is automatically downloaded daily into the ICEA database using an MS SQL Integration Services package.

MEASUREMENTS

Variables collected include basic demographic data, clinical history, present clinical information including vital signs and body weight, TB diagnostic results, haematological and chemistry laboratory results, medications, pharmacokinetic-related variables, adverse events, missed visits and TB treatment outcomes as defined by WHO (cure, completed, failure, default, loss to follow-up, death).[16] Details of these variables are presented in table 1.

Data quality control

Data quality control procedures are carried out for the data collected in the three databases: (1) All the data collected into ICEA, as per IDI standard procedures, are validated daily by a quality control officer who ensures that the data are complete and consistent. (2) All the data entered in the DataFax database are retrieved and validated by a verifier. In addition, the DataFax team generates weekly reports, which show the follow-up status of all patients enrolled and summarise all errors flagged by the verifiers. (3) Double entry is made into the EpiData database and the duplicate entry is then compared using the EpiData designated command; where errors are indicated, the entry is reassessed.

Data management and linkage of databases

The integrated SOUTH dataset is housed on the IDI server in the MS Excel format. The dataset is managed and merged by the study data manager and checked for completeness and accuracy every 3 months.

Details of the identifiers from different datasets used to link the collected data are available in the additional material section (online supplementary appendix). Each box displays the unique identifiers used to link the different databases, while the numbers in the boxes indicate the linkage ‘step number’.

The dataset are backed up in accordance with the existing data backup procedures; only the data manager has primary access and rights to manage the dataset to allow blinding of the study staff.

Drugs

Dosing of anti-TB drugs is done according to WHO guidelines using fixed-dose combinations; three tablets of RHZE (rifampicin, isoniazid, pyrazinamide and ethambutol) or HR (isoniazid and rifampicin) are prescribed if the patient’s weight was <55 kg, four tablets of RHZE or HR if weight was ≥55 kg and five tablets of RHEZ or RH if weight was ≥70 kg. All attempts are made to use the same

Table 1 Type and description of the variables collected in the Study on Outcomes related to TB and HIV drug Concentrations in Uganda study

Type of variable	Variables	Visit	Database
Basic demographics	Gender, age, address, phone contact	Enrolment	ICEA
Epidemiological	Tribe, marital status	Enrolment	ICEA
Clinical history	Date and result of HIV-positive result, date of enrolment into care, history of kidney and liver disease, herb use, smoking and alcohol consumption	Enrolment	ICEA
Clinical information	Present symptoms and duration (days), physical examination	Enrolment, week 2, 8, 24	DataFax
TB diagnostic	Sputum microscopy, Xpert MTB/RIF*, culture results, chest X-ray features,† drug sensitivity test‡	Enrolment, week 2, 8, 24	DataFax
Other laboratory results	Full blood count, liver enzymes, renal function, CD4 count§, viral load ¶	Week 2, 8, 24	MUJHU lab
Medications	ART, TB drugs, ART adherence, anti-TB drugs adherence, ART side effects, anti-TB drugs side effects, comedications including herbal use	Week 2, 8, 24	ICEA, DataFax
Pharmacokinetic-related variables	Time of last dose of anti-TB drugs and of last food intake, duration of treatment, time, accession number, drug concentrations	Week 2, 8, 24	DataFax, Pharmacokinetic Access database
Adverse events	Description, severity, duration, relation to study drug, relation to disease, action taken, outcome	At time of occurrence	DataFax
Missed visit	Phone and home visit tracking attempts, tracking outcome, reason for missed visit	At time of occurrence	DataFax
Outcomes	TB resolution, Treatment outcome (completed or cured, treatment default, treatments failure, death, relapse, lost to follow-up, other**	At week 24 or at the time of outcome occurrence	ICEA, DataFax

*Xpert MTB/RIF only at enrolment.
†Presence or absence of infiltrates, cavities, adenopathy, pleural and pericardial effusion.
‡If positive culture.
§CD4 count only at enrolment and week 24.
¶At enrolment if on ART, at week 24 if not on ART at enrolment.
**Withdrawn from the study, relocated/transferred out, stopped anti-TB treatment for clinical reasons.
ART, antiretroviral treatment; ICEA, Enterprise Clinical Electronic Application; lab, laboratory; MUJHU, Makerere University John Hopkins University; TB, tuberculosis.

brand, Strides-Arco, of the anti-TB drugs throughout the study, however, due to interruption in supplies, we used the Cosmos brand of RH (150/75 mg) from May 2014 for 5 months and the Svizera Labs brand (150/75 mg) from October 2014 onwards. Dissolution studies were done in the biochemistry laboratory at the University of Zurich (UZH) to ensure consistency in the composition of the drugs. Patients who were on protease inhibitors are given rifabutin (Mycobutin) 150 mg three times weekly instead of rifampicin.

Diagnostics

Direct and concentrated sputum microscopy is performed with auramine stain, and sputum cultures using both Löwenstein-Jensen (LJ) and BACTEC MGIT 960. In patients who fail to spontaneously provide a sputum sample, sputum induction is performed. Initially Xpert MTB/RIF (Cepheid) was performed at baseline in patients who have two negative sputum smear results; however, from June 2014 following a change in WHO and IDI guidelines, Xpert MTB/RIF is offered as a first diagnostic test in all patients suspected to have TB.

Drug concentration measurement

At each time point, 10 mL of serum is collected in BD VacutainerRapid Serum Tube, separated by centrifuging within 1 hour of the blood draw and stored at −80°C. Serum concentrations of rifampicin, ethambutol and isoniazid are later measured on site using ultraviolet high-performance liquid chromatography (UV-HPLC).

The UZH developed assays for the measurement of serum levels of (1) ethambutol, (2) rifampicin/rifabutin/moxifloxacin, (3) pyrazinamide/isoniazid (4) atazanavir, efavirenz and lopinavir (as single assays) using an analyser identical to the one at IDI: a. A Ugandan laboratory technologist was trained at UZH for 2 weeks on these methods. Assays were subsequently validated and implemented at IDI over a period of 7 months. The pharmacokinetic results generated by HPLC-UV are entered into an Excel spreadsheet and the drug concentration

Table 2 No of aliquots of serum collected (by November 2015)

Visit no	Patients with samples available	Available stored serum aliquots per visit	Total no of serum aliquots stored
Week 2	252	9	2268
Week 8	227	9	2043
Week 12	35	9	315
Week 24	153	9	1377

is calculated for each sample using manual calibration curve.

We collect three blood samples per study visit, and each sample is divided into three aliquots of up to 1 mL each, and are used for pharmacokinetic analysis for the various anti-TB drugs (nine aliquots per study visit). Table 2 below shows the number of patients with available aliquots for pharmacokinetic analysis of anti-TB drugs by November 2015. The laboratory technician has so far run 5099/6003 (85%) pharmacokinetic assays on stored blood aliquots, 1999 for isoniazid and pyrazinamide, 2001 for rifampicin and 1099 for ethambutol.

Cohort characteristics

From May 2013 to April 2015, a total of 294 patients were screened, of which 26 were excluded from the study. The main reasons for exclusions were having a history of TB (nine patients), four had only extrapulmonary TB, three had a GFR<50 mL/min; other reasons are shown in figure 1.

A total of 268 patients have been enrolled in the study, of which 71 were enrolled in the first calendar year, 140 in the second calendar year and 57 in the last calendar year (figure 2).

The majority of the patients are male (57.8%), the median age is 34 (IQR 29–40). The median time between the diagnosis of HIV and the diagnosis of TB is 2 months (IQR 0–22.5). The majority of the patients are ART naive (75.4%). The median CD4 cell count at enrolment is 163 cells/μL (IQR 46–298) with 57.5% having a CD4 cell count <200 cells/μL. All patients have had at least one index symptom for TB, with the vast majority (258, 97%) reporting cough for at least 2 weeks.

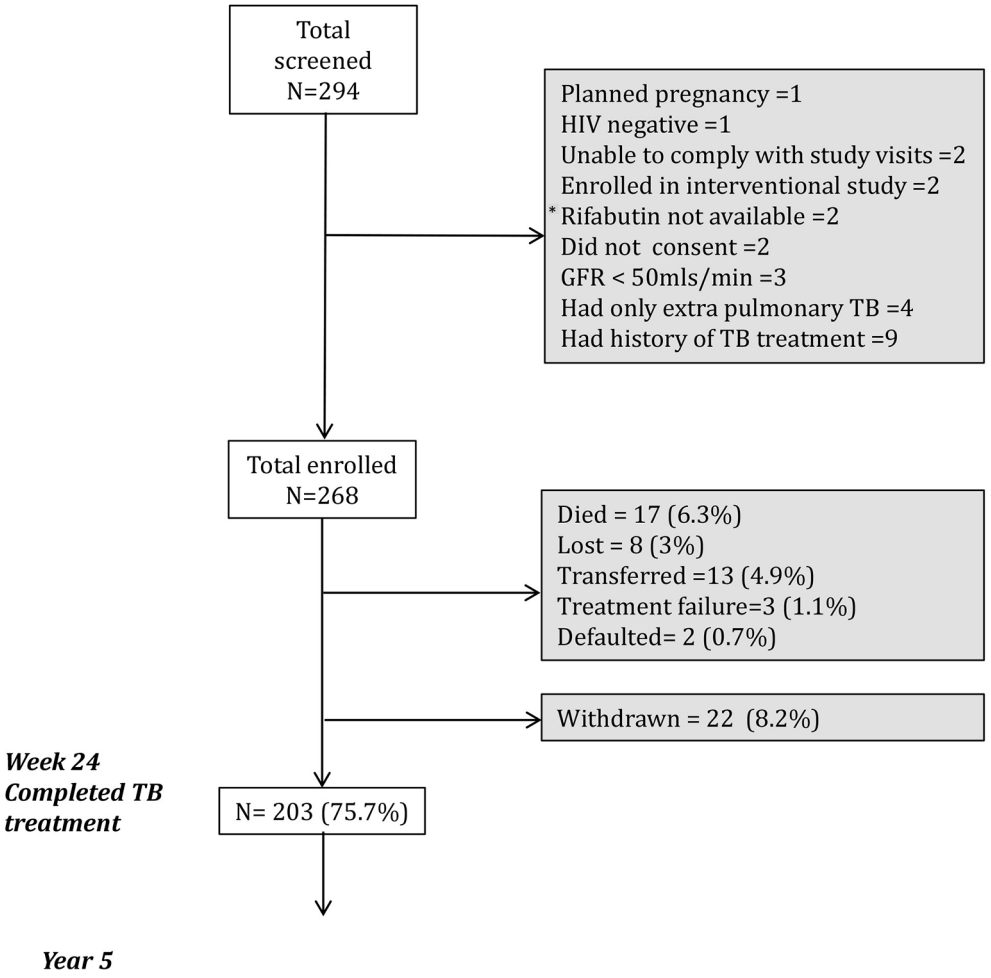

Figure 1 Follow-up status of the cohort. Number of patients who were screened, enrolled, withdrawn and followed up. *Patients were on protease inhibitor-based antiretroviral therapy. GFR, glomerular filtration rate; TB, tuberculosis.

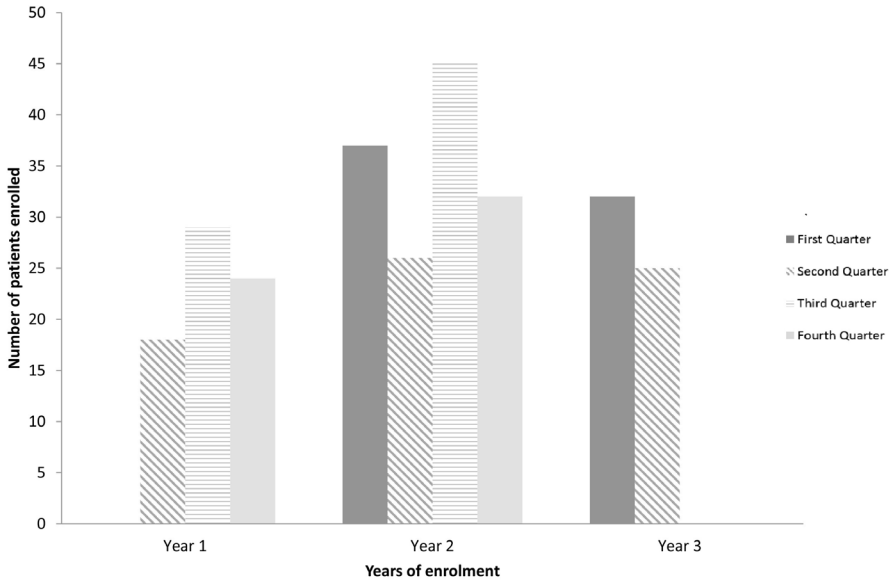

Figure 2 Number of patients enrolled each quarter. Number of patients enrolled in each year from year 1 to year 3.

Other detailed demographic, epidemiological characteristics are shown in table 3.

Figure 1 also shows the follow-up status of the 268 patients enrolled. Seventeen (6.3%) died, 3 (1.1%) had a positive sputum smear after 5 months of treatment and therefore defined as TB treatment failure, 2 (0.7%) defaulted from TB treatment, 13 (4.9%) were transferred to other public facilities in Kampala on patient's request, 8 (3%) were lost to follow-up and 22 (8.2%) were withdrawn from the study while on TB treatment before completing week 24. The reasons for withdrawal include: ART failure (two) necessitating switch to second-line ART, pregnancy (one), renal failure (three), liver toxicity necessitating interruption in TB treatment (five), drug resistant strains of TB (eight), TB meningitis (one), efavirenz toxicity necessitating switch to nevirapine (one), based on the medical judgement of the clinician (one). Of the 203 (75.7%) patients who completed TB treatment and are now in the routine follow-up phase for 5years, 3 (1.1%) died, 10 (3.7%) were transferred, 7 (2.6%) were lost to follow-up and 1 (0.4%) was withdrawn from the study.

TB diagnosis

Table 4 presents the results of the TB diagnostic tests of the patients enrolled in the study: 249 (92.9%) had a diagnosis of TB confirmed by sputum microscopy, Xpert or culture (microbiologically confirmed TB); 215 (80.2%) patients were culture positive and of those who were culture negative, 10 (3.7%) were Xpert/RIF positive and 13 (4.9%) was smear positive. Eleven (4.1%) patients had contaminated culture results and were diagnosed by a positive smear 7 (2.6%) and Xpert/RIF 4 (1.5%) only. Nineteen (7.1%) patients were clinically diagnosed. Xpert/RIF was performed in 138/268 patients of whom 126 were positive. Patients were categorised as sputum smear positive if the sputum microscopy results were positive at baseline or week 2.

Planned substudies

This population of patients will be followed up for a period of 5 years. The SOUTH cohort has been established with the aim of providing an ideal research platform for additional study questions and for fostering new collaborations.

During the course of the study a number of substudies have been planned and are under implementation, including:

1. Efavirenz concentration measurement. This study will be conducted on stored samples with the aim of describing the serum levels of efavirenz taken with concomitant anti-TB drugs and evaluating the association with toxicity
2. Viral load test: since routine viral load monitoring had not been implemented at the time of the set-up of the study, viral load measurement will be measured on stored samples to evaluate the proportion of patients with detectable viral load after 6 months of ART. Patients with a detectable viral load will be referred to the clinician-in-charge for counselling and evaluation for a switch to second-line ART.
3. Radiological evaluation study: we will perform evaluation of all chest X-rays and correlate radiological

Table 3 Patients' characteristics at cohort enrolment

Characteristics	N=268
Gender, males, n (%)	157 (58.6)
Age, years (median, IQR)	34 (29–40)
Months from HIV to TB diagnosis, median (CI)	2 (0 to 22.5)
BMI	
Median (CI), kg/m^2)	19.2 (IQR 17.7–21.7)
<18	76 (28.4%)
CD4 count	
Median (CI), cells/µL	163 (46 to 298)
<200 cells/µL, n (%)	149 (57.5)
<50 cells/µL, n (%)	66 (25.5)
ART	
Naive, n (%)	202 (75.4)
First line, n (%)	63 (23.5)
Second line, n (%)	3 (1.1)
Symptoms, n (%)	
Cough for at least 2 weeks	258 (97.0)
Fever	225 (84.6)
Night sweats	208 (78.2)
Weight loss	244 (91.7)
History of liver disease, n (%)	1 (0.4)
History of kidney disease, n (%)	1 (0.4)
Herbal use, n (%)	61 (22.8)
Smoking history, n (%)	19 (7.1)
Alcohol consumption, n (%)	35 (13.1)

ART, antiretroviral therapy; BMI, body mass index; TB, tuberculosis.

changes with anti-TB drug concentrations and TB treatment outcome.

4. Intensive pharmacokinetic study: we will carry out intense pharmacokinetic analysis at more time points in a subset of patients to describe their exposure to the anti-TB drugs over a 24-hour period.
5. Pharmacogenetic analysis: in collaboration with the University of Turin (Italy) a laboratory technician has been trained to carry out pharmacogenetic analysis on the stored blood samples. We will be able to correlate serum drug concentrations and outcome while taking into consideration the genetic variability of our population.

Table 4 Results of the tuberculosis diagnostic tests of the patients enrolled in the study

	Test description n (%)	
	Culture+	Culture−
Smear+	175 (65.3)	14 (5.2)
Smear−	40 (14.9)	27 (10.1)

+, positive; −, negative.

FINDINGS TO DATE

In this paper, we have documented the set-up of a large, well-characterised cohort of adults coinfected with TB/HIV with multiple datasets; detailed clinical, microbiological, radiological and pharmacokinetic information provides a resourceful platform for undertaking current and future studies in this population. It is also one of the largest pharmacokinetic datasets collected prospectively among patients coinfected with TB/HIV.

The majority of patients in this cohort had severe immunosuppression with a CD4 cell count of <200 cells/µL and about a quarter of them had a CD4 cell count less than 50 cells/µL. This population is consistent with those most at risk of TB infection. Furthermore, over 75% of the patients were ART naive when diagnosed with new pulmonary TB demonstrating the late presentation and initiation of ART in this population. Whether only patient factors led to late presentation or a limitation in access to specialised HIV care in this resource-limited setting contributed to the late initiation of ART remains unknown.

Despite the well-known challenges clinicians are faced with when diagnosing TB, especially in patients with HIV infection, we achieved microbiological confirmation of TB in 90% of our patients. This was possible by using several methods including sputum microscopy, culture and Xpert MTB/RIF. In the routine clinical setting in a resource-limited country this is not always possible and TB is therefore often time diagnosed clinically.[17]

The mortality rate among this cohort of patients while on TB treatment (6.3%) is similar to that reported countrywide mortality (6.4%),[18] regardless of the controlled environment in the study setting. On the other hand, and as expected in a study setting, the loss to follow-up rate during TB treatment is much lower (3%) than in our routine clinical setting (10%)[11] due to the deliberate attempts made to track patients and ascertain their outcome.

The main objective of this study is to determine the association between anti-TB drug concentrations and treatment outcomes. There are several factors that may affect anti-TB drug concentrations, for example, poor adherence, male sex and low BMI have been associated with low anti-TB drug concentrations. Drug–drug interactions may also lead to variation in anti-TB drug concentrations, for example, McIlleron *et al* reported a transient increase in pyrazinamide and ethambutol concentrations in the first few weeks following ART initiation which may contribute to hepatotoxicity while a decrease in rifampicin concentrations was observed. These, however, were not statistically significant.[4] Rifampicin, due to its CYP450 enzyme induction effect leads to a decrease in concentrations of the most commonly used non-nucleoside reverse transcriptase inhibitors (nevirapine and efavirenz).

Patients with HIV infection have been found to have low anti-TB concentrations due to malabsorption.[5] Several authors have found that low anti-TB drug concentrations (pyrazinamide, rifampicin and isoniazid) were associated with poor TB treatment outcomes[7 13 19 20] while others did not.[8 21 22] Many of these studies were retrospective with small sample sizes and only a few included patients with HIV infection. This is an aspect that this study will explore further and contribute to the existing studies by providing prospectively collected data with a considerably large sample size including a population of severely immunosuppressed patients coinfected with TB/HIV who at a particularly high risk of poor TB treatment outcomes. Aside from drug concentrations, we will be able to explore how other factors that may affect TB treatment outcomes in our population including low CD4 cell count, bacillary load and bilateral radiological disease.

TB is a known driver of HIV progression and vice versa; while patients with HIV have more severe presentations of TB and worse TB treatment outcomes (including death) compared with those without HIV, TB leads to increased transcriptional activity of HIV virus and therefore progression of HIV disease.[23] The SOUTH cohort is a unique asset to determine long-term outcomes of patients coinfected, and to answer relevant clinical questions on HIV-positive patients with a diagnosis of TB. Because TB may serve as a marker of severe immunosuppression, patients with a history of TB have decreased long-term survival and a higher incidence of new AIDS-defining opportunistic infections compared with those with no history of TB.[24 25] This study population of severely immunosuppressed patients will enable us to characterise these long-term outcomes further.

We have described the assembling of a large, well-characterised TB/HIV coinfection cohort with multiple datasets including pharmacokinetics. This cohort will facilitate our group's contribution to the characterisation of the association between TB treatment outcomes and serum drug concentrations of first-line anti-TB medications. Furthermore, it provides an excellent platform for a variety of planned substudies including pharmacogenetics.

STRENGTHS AND LIMITATIONS

The strength of this cohort lies in its relatively large sample size. In addition, pharmacokinetic data are collected prospectively and at three time points and on three different occasions which enables us to estimate the maximum concentrations better.

The limitation of this study is that directly observed therapy is only performed on the study visit and not throughout the course of TB treatment. Adherence to treatment between study visits relies may affect drug concentrations; however, data on adherence is collected.

COLLABORATION

Data from this cohort will be available on reasonable request and with permission of Infectious Diseases and UZH collaboration. Collaboration with other researchers with interest in pharmacokinetic research in patients coinfected with TB/HIV is encouraged and can be sought through the Infectious Diseases—UZH collaboration.

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Contributors JF, NC and ML contributed to the conceptualisation of this protocol. CS-W and BC contributed equally to writing this paper. AB, CS-W, AB, DM, UG and LH contributed to the data collection, JM and BL contributed to the data management and analysis, AK and JF supervised the writing of this paper and all authors read and approved the final version of this paper.

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Competing interests None declared.

Patient consent Obtained.

Ethics approval The SOUTH study was approved by the Joint Clinical and Research Centre Committee ethics committee and the Uganda National Council for Science and Technology (Number HS 1303).

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement The data that support the findings of this study are available from the corresponding author (CS-W) but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are, however, available from the authors on reasonable request and with permission of Infectious Diseases and University of Zurich collaboration.

REFERENCES

1. Perriëns JH, Colebunders RL, Karahunga C, *et al*. Increased mortality and tuberculosis treatment failure rate among human immunodeficiency virus (HIV) seropositive compared with HIV seronegative patients with pulmonary tuberculosis treated with 'standard' chemotherapy in Kinshasa, Zaire. *Am Rev Respir Dis* 1991;144:750–5.
2. Dworkin MS, Adams MR, Cohn DL, *et al*. Factors that complicate the treatment of tuberculosis in HIV-infected patients. *J Acquir Immune Defic Syndr* 2005;39:464–70.
3. Peloquin CA, Nitta AT, Burman WJ, *et al*. Low antituberculosis drug concentrations in patients with AIDS. *Ann Pharmacother* 1996;30:919–25.

4. McIlleron H, Rustomjee R, Vahedi M, *et al*. Reduced antituberculosis drug concentrations in HIV-infected patients who are men or have low weight: implications for international dosing guidelines. *Antimicrob Agents Chemother* 2012;56:3232–8.
5. Gurumurthy P, Ramachandran G, Hemanth Kumar AK, *et al*. Malabsorption of rifampin and isoniazid in HIV-infected patients with and without tuberculosis. *Clin Infect Dis* 2004;38:280–3.
6. World Health Organisation. Tuberculosis fact sheet. 2015 http://www.who.int/mediacentre/factsheets/fs104/en/
7. Sloan DJ, Schipani A, Waterhouse D. Pharmacokinetic variability in TB therapy: associations with HIV and effect on outcome. *Conference on Retroviruses and Opportunistic Infections*; 3-6 March 2014, Boston, Massachusetts: Hynes Convention Center, 2014.
8. Park JS, Lee JY, Lee YJ, *et al*. Serum Levels of antituberculosis drugs and their effect on tuberculosis treatment outcome. *Antimicrob Agents Chemother* 2015;60:92–8.
9. Burhan E, Ruesen C, Ruslami R, *et al*. Isoniazid, rifampin, and pyrazinamide plasma concentrations in relation to treatment response in Indonesian pulmonary tuberculosis patients. *Antimicrob Agents Chemother* 2013;57:3614–9.
10. Nwaka S, Ochem A, Besson D, *et al*. Analysis of pan-African centres of excellence in health innovation highlights opportunities and challenges for local innovation and financing in the continent. *BMC Int Health Hum Rights* 2012;12:11.
11. Hermans SM, Castelnuovo B, Katabira C, *et al*. Integration of HIV and TB services results in improved TB treatment outcomes and earlier prioritized ART initiation in a large urban HIV clinic in Uganda. *J Acquir Immune Defic Syndr* 2012;60:e29–35.
12. Castelnuovo B, Hermans S, Park R, *et al*. Evaluation of the impact of TB-HIV integrated care in reducing the proportion of patients defaulting anti TB treatment in a large urban HIV clinic in Kampala, Uganda. *Proceedings of the Sixth IAS Conference on HIV Pathogenesis, Treatment and Prevention*; 17-20 July 2011, Rome, Italy. (TUPE472), 2011.
13. Chideya S, Winston CA, Peloquin CA, *et al*. Isoniazid, rifampin, ethambutol, and pyrazinamide pharmacokinetics and treatment outcomes among a predominantly HIV-infected cohort of adults with tuberculosis from Botswana. *Clin Infect Dis* 2009;48:1685–94.
14. World Health Organisation. *Guidelines for treatment of tuberculosis*. 4th edition, 2010.
15. Castelnuovo B, Kiragga A, Afayo V, *et al*. Implementation of provider-based electronic medical records and improvement of the quality of data in a large HIV program in Sub-Saharan Africa. *PLoS One* 2012;7:e51631.
16. World Health Organization. Guildelines for treatment of tuberculosis. 2013.
17. Lawn SD, Wood R. Tuberculosis in antiretroviral treatment services in resource-limited settings: addressing the challenges of screening and diagnosis. *J Infect Dis* 2011;204(Suppl 4):S1159–67.
18. World Health Organisation. Global health observatory data repository. Tuberculosis. Mortality and prevalence. 2014 http://apps.who.int/gho/data/view.main.57020ALL?lang=en
19. Prahl JB, Johansen IS, Cohen AS, *et al*. Clinical significance of 2 h plasma concentrations of first-line anti-tuberculosis drugs: a prospective observational study. *J Antimicrob Chemother* 2014;69:2841–7.
20. Pasipanodya JG, McIlleron H, Burger A, *et al*. Serum drug concentrations predictive of pulmonary tuberculosis outcomes. *J Infect Dis* 2013;208:1464–73.
21. Requena-Méndez A, Davies G, Waterhouse D, *et al*. Effects of dosage, comorbidities, and food on isoniazid pharmacokinetics in Peruvian tuberculosis patients. *Antimicrob Agents Chemother* 2014;58:7164–70.
22. McIlleron H, Watkins ML, Folb PI, *et al*. Rifampin levels, interferon-gamma release and outcome in complicated pulmonary tuberculosis. *Tuberculosis* 2007;87:557–64.
23. Toossi Z, Mayanja-Kizza H, Hirsch CS, *et al*. Impact of tuberculosis (TB) on HIV-1 activity in dually infected patients. *Clin Exp Immunol* 2001;123:233–8.
24. Whalen C, Horsburgh CR, Hom D, *et al*. Accelerated course of human immunodeficiency virus infection after tuberculosis. *Am J Respir Crit Care Med* 1995;151:129–35.
25. Chu R, Mills EJ, Beyene J, *et al*. Impact of tuberculosis on mortality among HIV-infected patients receiving antiretroviral therapy in Uganda: a prospective cohort analysis. *AIDS Res Ther* 2013;10:19.

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Cohort profile of a study on outcomes related to tuberculosis and antiretroviral drug concentrations in Uganda: design, methods and patient characteristics of the SOUTH study

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