Protocol

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Tuberculosis among HIV-positive patients:
an international prospective observational study

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1. STUDY BACKGROUND AND RATIONALE

1.1. Background

Tuberculosis (TB) is the most frequently occurring coinfection and the leading cause of death among HIV-positive patients worldwide. (1) The convergence of the tuberculosis (TB) and HIV epidemics has substantially increased the incidence, difficulty of diagnosis, and associated mortality of TB, and in turn, TB accelerates the progression of the HIV disease. (2;3) Increasing rates of drug resistance, including the emergence of multi-drug resistant (MDR) and extensively drug resistant (XDR) TB, have greatly diminished the success rate of standard anti-TB therapy, which has particular implications for HIV-positive patients. (4)

The introduction of HIV-treatment (antiretroviral therapy (ART)) and consequent improvement of immune status of HIV-positive persons reduces the risk of developing TB by 70-90%. Nonetheless, TB continues to occur among HIV-positive persons, even among those responding to ART. (5-7)

The interaction of TB and HIV and the best way to manage these two life-threatening diseases present major clinical and public health challenges and are priority research areas worldwide. (2) Treatment of HIV/TB is a great challenge because patients are simultaneously prescribed at least 2-4 TB drugs for at least 6 months in addition to their lifelong HIV-treatment of a minimum of 3 drugs per day. This can result in multiple toxicities and adherence issues due to potential interactions between HIV and TB drugs, overlapping metabolic pathways, and the uncertainty of when best to initiate HIV treatment in relation to TB therapy, particularly in patients with advanced HIV-infection.(3;8) Initiation of ART shortly after TB therapy has been started is now recommended (3;8;9), however the impact of ART and TB drug interactions is not fully understood. In addition, initiation of ART in such patients is often complicated by an immune reconstitution inflammatory syndrome (IRIS), which is difficult to diagnose, manage and may even have a fatal outcome. (10) At present there is a lack of robust evidence on the most optimal management of HIV-TB patients and most treatment guidelines rely on expert opinions.

Although there are currently a number of ongoing clinical studies in African and Asian populations addressing the challenges of HIV/TB coinfection, such studies in Europe remain scarce. It is crucial to fill this gap in European research as 12 of the 14 countries most affected by MDR-TB in the world are in the European region. (4) Countries most affected by MDR-TB (i.e. Eastern European countries) have TB incidence rates comparable to those in Africa, and the European region's overall treatment success rate is the same as that in Africa (4,11). Furthermore, while TB rates have decreased in most of Western Europe over the past 10 years, rates have increased in Eastern Europe (11). The latter may be a particular threat for a widespread epidemic across the continent due to expansion of the European Union to the east and the increasing rate of migration within Europe.

Results of the retrospective phase (2004-2006) of the HIV/TB collaborative study (www.cphiv.dk/HIVTB) have documented a 3 to 5-fold higher mortality within the first

year after TB diagnosis in Eastern compared with Western Europe. (12) The underlying reasons for this difference, and whether this regional difference will persist, remains a significant research question. There were marked regional differences not only in the clinical characteristics of HIV/TB patients and the level of MDR-TB, but also in the management of these patients, namely usage of the individual anti-TB drugs and ART. Importantly, there was a clear association between the clinical prognosis and a weighted score based on access to and use of health care indices (HCI) such as use of TB diagnostics, assessment of anti-TB drug resistance, type of initial TB regimen, and time of initiation of cART. In general, the chances of a successful treatment outcome were significantly higher in patients with a higher HCI score, and the average HCI score for patients in Eastern Europe was significantly lower than elsewhere. (13) The proposed HCI score provides a tool for future research and monitoring TB-treatment in individual HIV-patients, and the individual HCIs may serve as a benchmark to assess and improve management of HIV/TB coinfection in Europe and elsewhere.

We plan to explore these findings further in a prospective extension of the already existing HIV/TB collaboration and assess whether improvement in health care utilisation and HCI score increase will eventually lead to improved survival.

1.2. Scientific and social impact of study outcome

This will be the first prospective study of HIV/TB coinfection across Europe. The establishment of such a cohort will allow for monitoring the patterns of the epidemic across the continent, which will have important clinical and public health implications. Due to the prospective design, this study will further add to the understanding of the nature of HIV/TB coinfection and help to improve/optimise treatment of HIV/TB patients by establishing a benchmark for use of health care interventions, thus identifying aspects that require improvement. (13) The present study will lead to enhanced knowledge of the epidemiology and clinical issues related to HIV/TB coinfection, and will have relevance for HIV/TB patients both within and outside Europe. Prospective data will allow for analyses of whether improvement in HCIs will eventually lead to better results in countries with low rates of successful treatment outcome.

The study will enrich evidence on as of yet unresolved issues such as influence of MDR and XDR and choice of anti-TB regimens, initiation of ART and management of anti-TB and ART drug interactions and management of IRIS, thereby improving the prognosis of HIV/TB patients.

Patients with TB in Western Europe are predominantly migrants from high-prevalence countries. Collection of mycobacterial specimens will facilitate epidemiological analysis of *Mycobacterium tuberculosis* isolates allowing comparison of strains from different parts of Europe with regard to transmission and identification of strains with particular properties (high infectivity, virulence and resistance). This analysis will also enable characterisation of infectious clonality, tracking of individual strain movement and identification of mutations associated with resistance to key anti-TB drugs.

The uniqueness of this study is that it will enrol a significant number of HIV/TB patients from Eastern Europe, the European region mostly affected by both epidemics.

The paucity of HIV/TB cohorts and published data from this region underscores the importance of the proposed research. In addition, a representative sample of patients will be enrolled from Argentina and potentially other middle-income countries from South America, which also will increase the heterogeneity of the study and provide even more power to the study. By establishing a cohort of HIV/TB patients, this study will also provide an important surveillance tool, which can be further used by national and international authorities. In addition, it will contribute to the improvement of management of HIV/TB patients by enhancing collaboration between HIV and TB specialists, which continues to be a barrier for optimal health care utilisation in many places across Europe.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study objectives

To prospectively study the long-term clinical prognosis of HIV-positive patients with active TB disease across Europe, temporal changes and regional differences hereof.

The specific objectives, falling into two main categories: 1) epidemiology of HIV/TB coinfection 2) clinical aspects and management of HIV/TB patients

1) Describe temporal changes and regional differences in clinical characteristics and management of HIV/TB patients, including:
   a) Estimate prevalence of MDR- and XDR-TB in HIV/TB patients across Europe
   b) Monitor temporal changes in health care utilisation for HIV/TB patients and in clinical prognosis and thereby validation of Health Care Index score as prognostic indicator
   c) Establishment of a repository of *Mycobacterium tuberculosis* samples for centralised genetic sequencing and analysis of anti-TB drug resistance

2) Management of HIV-positive patients with active TB disease in regards to:
   a) Most optimal TB drugs and treatment duration
   b) Specific TB and ART drug combinations in regards to efficacy, toxicity and drug-drug interactions
   c) Role of MDR- and XDR-TB in long-term clinical outcome, including relapse rate of TB and most optimal management of patients with MDR- and XDR-TB
   d) Incidence of IRIS in relation to the time of ART initiation and management of TB-IRIS

2.2. Study Endpoints

The primary endpoint of this study is the outcome of TB disease, defined according to the World Health Organization standards and including: cure, treatment completed, treatment failure, defaulted/interrupted treatment, transferred out/lost to follow-up, death. (14)

The **secondary** endpoint is TB reappearance rate, including both relapse of a previous TB case and reinfection with a new mycobacterial strain.

3. INVESTIGATIONAL PLAN

3.1. Study design

The HIV/TB collaborative study is an international prospective observational cohort study. The study infrastructure has already been established during the retrospective phase, which included 4 national HIV cohorts and 36 clinics from 11 European countries (5 from Eastern Europe) and Argentina, and all participating cohorts/clinics have experienced interest in continuing collaboration prospectively.

3.2. Study population

The study will include all consecutive HIV-patients (or an unbiased subgroup) developing active TB disease at the participating sites and maintain patients under continuous follow-up. In Western Europe, HIV/TB patients will be identified within the existing national and/or regional HIV cohorts or by HIV-specialists in the Infectious Disease departments. In Eastern Europe, HIV and TB clinics are usually separate units; therefore data will be collected from both sources. This framework has worked well for the retrospective phase of the study.

3.3. Inclusion criteria

Eligible patients are HIV-positive persons >16 years under prospective follow-up within a participating cohort/clinic, in whom a definite or presumptive TB diagnosis has been established after January 1st 2011 and irrespectively whether TB treatment has been initiated or not.

3.4. Exclusion criteria

- Patients under 16 years of age
- Absence of documented HIV-1 infection (tests performed up to **3 months** after the T B diagnosis are accepted)
- Patients with presumptive diagnosis of TB in whom TB treatment was stopped and TB diagnosis was ruled out

3.5. Treatment during study

As the HIV/TB study is an observational study, treatment will not be influenced by the study. Patients remain under guidance and treatment of their personal physician.

4. MEASUREMENTS AND EVALUATION

4.1. The operational definition of TB:

- **Definite TB** - a case of TB documented by microscopy and/or culture/ PCR.

- **Presumptive TB** - a case, in which anti-TB therapy is initiated and not subsequently stopped because the TB diagnosis is ruled out, or in which caseous granuloma is found in biopsy material.

4.2. Data collection on TB and HIV

The first data collection will be within the first months after the date of TB diagnosis (**Baseline**). Data will be collected based on local routine data collection on a specially designed standardised case report form (CRF) for TB and HIV respectively. The following detailed information will be collected at this time point:

– Demography data
– Previous screening for TB, anti-TB prophylaxis and vaccination
– Previous TB-disease
– Symptoms and duration of symptoms for the current TB case
– Diagnostic procedures for the current TB case, including smear microscopy, culture, resistance and PCR/ DNA tests
– Clinical presentation of current TB and whether the case is considered to be IRIS
– Laboratory assessments
– Initial choice of anti-TB drugs
– Characterisation of the underlying HIV-infection including CD4 cell counts and HIV-RNA measurements, ART history and AIDS defining diagnoses (for sites where HIV data are already stored in an electronic format, there will be a possibility for electronic data transfer).

Thereafter data will be collected at 6, 12 and 24 months using updated CRFs with an aim of an average follow-up of 2 years after Baseline. This will enable us to examine long-term progression, including TB relapses and the role of MDR-TB. Information collected at follow-up will focus on clinical details of TB, patterns of anti-TB treatment and outcomes of TB disease, including information on MDR-TB, as well as characterisation of the underlying HIV-infection. Please see **appendix 1** for a sample CRF.

Practical details regarding data collection

Data collection and shipment of the CRFs to the sites and CRFs submission to the coordinating centre will be performed according to the standard procedures developed by coordinating centre and on 6-month basis. Data can be submitted by completing paper CRF or via electronic data transfer using HICDEP format (please see details on www.chip.dk).

4.3. Immune Reconstitution Syndrome

To address objective 2.d, a specially designed CRF detailing presentation and management of IRIS will be completed for patients suspected for development of TB as a consequence of immune reconstitution. The CRF is a modified version of the AIDS Clinical Trials Group (ACTG) IRIS CRF (www.actgnetwork.org). Questions included in the IRIS CRF are based on the recently published international criteria for IRIS diagnosis (15). Please see **Appendix 2** for a sample CRF.

4.4. TB and HIV Health Care

Information on HIV and TB health care infrastructure and services in a particular centre/country will be collected by using a specially designed questionnaire at the beginning of the study (primo 2011) and after 2 years (ultimo 2013). Each centre will be sent a questionnaire to be completed by a health care provider. Information to be

collected includes the local standards for: TB diagnostics, TB and HIV treatment, availability of 1st and 2nd line TB drugs and ARVs, integration of TB and HIV services, use of Directly Observed Treatment (DOT) strategy, procedures for TB screening among HIV-positive patients and HIV testing among TB patients, use of TB prophylaxis; availability of substitution therapy for IDUs and procedures for laboratory monitoring of HIV/TB patients. Please see Appendix 3 for a sample questionnaire form.

4.5. Mycobacteria samples

Additionally, if the centre is participating in *Mycobacteria* sample collection, mycobacterial specimens will be collected for each patient with culture positive for *Mycobacteria tuberculosis* and will be centrally analysed for susceptibility to TB drugs and for molecular characterisation using DNA fingerprinting technique. This will allow for characterisation of *Mycobacteria* clones in different parts of Europe and Argentina and detection of differences hereof. Centralised resistance test and DNA sequencing will allow for comparison of resistant and non-resistant *Mycobacteria* strains as well as quality assurance of resistance tests performed locally.

4.6. Sample size

Using a conservative approach and assuming an underlying mortality rate of 3 per 100 person-years of follow-up, loss to follow-up of 10%, and a follow-up of 24-27 months per patient, approximately 700 patients from Eastern Europe, 300 from Western Europe and 100 from Argentina (and potentially other countries in South America) will be required to provide 80% power and a type I error rate of 5% to detect a 2-fold difference in mortality. (12,16) The large numbers of patients included is important in allowing for sufficient power to study smaller subgroups of patients, such as those taking specific drug regimens, developing specific side effects, those in different regions of Europe, infected with MDR-/XDR-TB, etc.

4.7. Study milestones

Milestone no.	Expected result	Expected date
1	400 HIV TB coinfected patients enrolled	M12
2	400 HIV TB coinfected patients enrolled	M24
3	300 HIV TB coinfected patients enrolled	M36
4	Results presented (1 publication and 1 presentation)	M16
5	Results presented (1 publication and 1 presentation)	M26
6	Results presented (2 publications and 2 presentations)	M38
7	Results presented (2 publications and 2 presentations)	M52

4.8. Ethical Consideration

The HIV/TB project is an observational study and patients will not be exposed to any experimental interventions nor will the study intervene with the clinical management of the patient. The study will only collect information from patient records and if necessary, patient interview.

The study is conducted according to the current ethical standards including the WMA Declaration of Helsinki and will be submitted to the appropriate regulatory

authorities including ethical committees in the participating countries, as requested by local regulations.

When informed consent is required by the local and/or national Ethics Committees, this will be obtained prior to the initiation of any study related data being obtained. The consent form must be approved by the IEC/IRB of each participating centre.

The data storage and handling will be protected in accordance with and approved by The Danish Data Protection Agency (Datatilsynet) under the Act on Processing of Personal Data (Act No. 429 of 31 May 2000) and European Commission Directive 95/46/EC.

5. DATA ANALYSIS METHODS AND STUDY DELIVERABLES

5.1. General considerations

Ad Objective 1)

Describe temporal changes and regional differences in clinical characteristics and management of HIV/TB patients, including:
  a) *Prevalence of MDR- and XDR-TB in HIV/TB patients across Europe*
  b) *Monitoring of temporal changes in health care utilisation for HIV/TB patients and in clinical prognosis and thereby validation of HCI score as prognostic indicator*
  c) *Establishment of a repository of Mycobacteria tuberculosis samples for centralised genetic sequencing and analysis of anti-TB drug resistance*

Temporal trends will be assessed by comparing patients' characteristics, management of HIV/TB patients and their outcome with the results obtained during retrospective phase of the study in 2004-2006. (12) Health care provided to the HIV/TB patients will be assessed at the beginning of the study (2011) and at its final stage (2013). In addition, the health care index score as a prognostic indicator will be validated on several levels (i.e. individual patient, clinical centre, region) and compared across regions of Europe. The information regarding prevalence of MDR- and XDR-TB in HIV-positive patients across Europe is scarce (12). Identification of most affected areas and trends in the spread of drug-resistant TB will have important epidemiological implications.

Centralised genetic sequencing of *Mycobacteria* strains using DNA-fingerprinting technique will facilitate epidemiological analysis of TB epidemic across Europe allowing for a comparison of strains from different geographic areas and the tracking of the epidemiology of individual strains. This data will also enable characterisation of infectious clonality, identification of mutations associated with resistance to key TB drugs and identification of strains with particular properties (high infectivity, virulence and resistance). Finally, it might have important insights into the questions regarding TB reactivation versus reinfection.

Ad Objective 2)

Management of HIV-positive patients with active TB disease in regards to:
 a) *Most optimal TB drugs and treatment duration*
 b) *Specific TB and ART drug combinations in regards to efficacy, toxicity and drug-drug interactions*
 c) *Role of MDR- and XDR-TB in long-term clinical outcome, including relapse rate of TB and most optimal management of patients with MDR- and XDR-TB*
 d) *Incidence of IRIS in relation to the time of ART initiation and management of TB-IRIS*

The objectives outlined above will be addressed in relation to the study's primary endpoint (outcome of TB disease). The most optimal TB drug combinations and treatment duration will be determined by identifying those with the highest chances of successful outcome of the TB disease.

The strength of this analysis is that it will evaluate various drug combinations (TB, ARVs and TB-ARVs), as tooppposed to the evaluation of a single drug. Earlier cART initiation in TB-patients is now recommended, however the impact of drug interactions on long-term outcome is yet unknown. (8) In Eastern Europe, cART became widely available after 2006 (1); whether this has improved treatment efficacy and patients' survival is to be analysed. Further, barriers to implement and follow current international guidelines (17,18) on management of HIV/TB patients (including barriers to diagnose TB by culture and determine drug susceptibility), use RHZE treatment in all TB patients (with or without second line TB drugs in areas with high MDR-TB prevalence) and adherence to the TB treatment and cART will be assessed.

Incidence of MDR- and XDR-TB will be calculated and risk factors hereof will be determined and compared across regions in relation to patients' outcome.

Incidence of TB-IRIS will be calculated in all study populations as well as in various sub-groups (e.g. different regions, CD4 cell level, risk factors). Risk factors for development of IRIS and interventions to decrease the incidence will be determined. Diagnostic and management of TB-IRIS still present certain difficulties for clinicians, our cohort of HIV/TB patients may serve as an evaluation tool for recently established clinical criteria for IRIS (15).

5.2. Statistical analysis

Separate detailed statistical plans will be developed in collaboration with statisticians from the Research Department of Infection and Population Health, HIV Epidemiology and Biostatistics Group, UCL – Royal Free Campus, London, UK to address each of the objectives, which will be approved by the Steering Committee prior to analysis. The types of analyses to be performed include, but are not limited to, the examples described below.

Additional subprojects are strongly encouraged and all investigators are encouraged to submit proposals on such subprojects. The proposals will be evaluated and approved by the SC and ad-hoc groups will be organised as necessary.

For reasons of consistency, the statistical group in London will carry out all statistical analyses. Investigators involved in a given subproject can spend time with the statisticians in London and they can be involved in the statistical analyses under the supervision of the group in London.

Broadly, the characteristics of patients with TB, including existence of resistance to anti-TB drugs, will be described and compared according to geographical region, using descriptive statistics as well as multivariable models. Clinical outcomes will be determined and compared across regions, as will the influence of specific anti-TB drugs, the presence of MDR-TB and the timing of ART in antiretroviral naïve patients with active TB. Clinical outcome will be further analysed in multivariable Cox or Poisson regression models. Analyses will be developed to describe and investigate the patterns of ARVs and TB drugs, possible pharmacokinetic interactions and toxicities, including regional differences. Prevalence and incidence of IRIS in HIV/TB patients will be assessed for patients initiating cART. Multivariable Cox or Poisson regression models will be used to determine risk factors for IRIS. Temporal trends over time in mortality rates or other outcomes which, will be monitored at regular time intervals. Multivariable Poisson or Cox regression models will be used to assess the degree to which trends over time in death rates, for example, can be explained by changes in use of newer treatment regimens or other factors. Formal tests of interaction can be used to determine if changes in mortality rates vary from region to region.

5.3. Study Deliverables

Deliverables no.	Deliverables title	Submission date
1	Enrol 400 HIV-TB coinfected patients	M12
2	1 Abstract submitted for scientific meetings; 1 publication in peer-reviewed journal	M16
3	Enrol 400 HIV-TB coinfected patients	M24
4	1 Abstract submitted for scientific meetings; 1 publication in peer-reviewed journal	M26
5	Enrol 300 HIV-TB coinfected patients	M36
6	2 Abstracts submitted for scientific meetings; 2 publications in peer-reviewed journal	M38
7	2 Abstracts submitted for scientific meetings; 2 publications in peer-reviewed journal	M52

Scientific objectives of the abstracts and publications should be defined based on the study objectives (see section 2.1) as data become available and according to the HIV/TB research agenda worldwide and new evidence from other studies. The intention is to submit at least 6 abstracts and 6 publications during the 5-year study period (see table above).

6. STUDY ORGANISATION AND COORDINATION

6.1. Study Coordination

The study coordinating office is Copenhagen HIV Programme (CHIP), University of Copenhagen, Denmark. The work includes: formation of a central database, coordination

and collection of data from each of the cohorts/clinics to the central database, oversight of the cohort/clinic protocol compliance, review and query event forms in real time as well as monitoring visits, prepare a draft version of public communications from the study, provide recommendations to the Steering Committee (SC) for possible expansion of or exclusion from the study.

The Copenhagen HIV Programme has strong links to the HIV Epidemiology and Biostatistics group at University College London (UCL), UK, who will be responsible for the statistical analyses. This work will be lead by Professor Amanda Mocroft.

The staff within the study coordinating office consists of a study coordinator, data manager/assistant/supervisor of quality assurance (QA) programme and a statistician (from UCL). The workload for the study coordinator is estimated to be 25% of a full time position.

6.2. Study Governance

The study coordinating office will be supervised by the Steering Committee (SC). One representative from each cohort/country in Western Europe and one from each country in Eastern Europe will be members of the SC. The SC approves all analytic proposals prior to their execution, approves requests to publish results from the HIV/TB project and decides on exclusion of a cohort/clinic based on the criteria specified below.

The SC will have sole responsibility for the scientific conduct of the HIV/TB project. The Committee will expect allowance to review all publications within a defined and reasonable time frame, and will be expected to consider reviews as peer reviews.

The staff at the coordinating centre and the statistical centre will participate in the SC meetings, but will not have the right to vote.

The study coordinator assumes responsibility and guarantees that only authorised personnel have access to the study database and further that only analyses previously approved by the SC will be performed on the data set. The study database will remain at the coordinating centre and the statistical centre at all times. The ownership of the data set from each of the cohorts/clinic will always belong to the cohort/clinic that provided the data. All patients' data in the central database is provided by the cohorts/clinics in an anonymous form, and the coordinating office of the HIV/TB project will not be able to identify the patient at any time (only the cohorts/clinics can do this). Overlap of patients between cohorts will be avoided by procedures developed on a case-by-case basis.

All investigators actively involved in the HIV/TB project in the participating cohorts/ clinics will be part of the HIV/TB project study group (attachment 2).

6.3. Study funding

The study is funded by the European Commission through the FP7 and as per January 1st 2011 has been granted 480.000 euro. The current grant covers 5-year study period and includes study coordination and reimbursement for data collection for a minimum of 1100 HIV/TB patients in amount of 10 euro per TB CRF and 10 euro per HIV CRF. *Mycobacteria* samples will be reimbursed an amount of 30 euro per sample.

Applications for additional funding from other sources are encouraged and should be coordinated by CHIP.

6.4. Quality assurance

To ensure credibility of results generated as part of the HIV/TB project standardised quality assurance (QA) procedures will be implemented. The manual of operations (MOOP) will include regular visits (at least once annually) to the participating sites by a monitor not associated with the particular site and appointed by each cohort. All deaths and patients with MDR-TB will be reviewed as will a random sample of at least 10% of all patients participating in the HIV/TB project. During monitoring visits, training of site personnel will be conducted. A report on outcome of all monitoring visits will be sent to the study coordinating office together with the procedure of this selection and which records were reviewed. In addition, written material on training issues related to the HIV/TB project will be drafted by the study coordinating office.

Targets of the quality of the key data to be collected and performance tasks have been identified and described below. Should a participating site or a cohort coordinator under-perform according to this set of standards, the study coordinator is responsible for reporting this to the Steering Committee for consideration and possible exclusion.

6.5. Requirements of clinics and cohorts to participate

Before accepting a cohort/clinic in to the study, the following issues need to be addressed satisfactorily:

- Commitment to enrol consecutive patients with active TB, or using some other well-defined selection scheme, that avoids any possibility of selection of patients for inclusion based on the outcome of their TB.
- Commitment to continue follow-up of patients for two years after enrolment
- A reasonable size of currently followed patients on which relevant data described in detail in methods section (demography, clinical presentation of TB-disease, anti-TB treatment, microbiological characterisation of the TB-infection including resistance patterns, laboratory assessments and outcomes as well as characterisation of HIV-infection) are collected
- Ability to reliably collect data on the questions detailed above and supply of the coordinating office with these data
- Ability to implement quality assurance measurements as detailed above
- Acceptance of organisation and publication rules of the HIV/TB project
- Active scientific involvement is strongly encouraged

During the study, a cohort or clinic(s) within a cohort can be excluded for the following reasons (targets and levels at which there are serious concerns are indicated):

- Delay with data collection for more than 6 months
- Basic HIV- and/or TB data unreliably collected
- Non-compliance with providing protocol-indicated data

6.6 Publications

The intention is to announce results from the HIV/TB project in a coordinated and consistent manner in manuscripts to be submitted to peer-reviewed journals. The SC will decide the prioritised scientific questions to be addressed. Prior to the publications, preliminary results may be presented at specialised scientific conferences.

Persons who are centrally involved in the design and execution of the various tasks involved in the HIV/TB project (i.e. coordination, analysis, overall decision making, collection of data) will be co-authors on the scientific publications. In addition, co-authorships will be rotated fairly among the study investigators according to the number of patients included at the individual clinics/cohorts. SC members will be acknowledged in all publications and an appendix of all members of the HIV/TB project study group will be included.

If any of the cohorts/centres (or several cohort/centres) decide to report on issues related the research questions that the HIV/TB project aim to address on their own, the SC should be notified as soon as possible and at least 4 weeks before public disclosure, for the purpose of allowing the SC to prepare a response based on joint data set prior to public disclosure. However, data provided by a particular cohort/centre remains a property of this particular cohort/centre and publications on individual data set are encouraged.

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