Research Priorities for HIV/M. tuberculosis Co-Infection


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Abstract: This document summarizes priority areas for joint research and concerted actions to counteract the public health threat of AIDS/TB as identified within the European Support Action “EUCO-Net” funded under the 7th Framework Programme of the European Commission.

Keywords: Research priorities, pathogenesis, HIV/M. tuberculosis co-infection, treatment, prevention, diagnostics, EUCO-Net.

INTRODUCTION

Key WHO policy documents have identified priorities for handling HIV/AIDS and TB. On the HIV/AIDS side, the document is aimed at pursuing the goal of “universal access to comprehensive prevention programs, treatment, care and support” by the year 2010 [1]. On the TB side, the “Stop TB Strategy”, wishes to ensure universal access to high-quality...
diagnosis and patient-centred treatment for all TB patients (including those co-infected with HIV and harbouring multidrug resistant (MDR) and extensively drug resistant (XDR) TB strains), and to support the development of new and effective tools to prevent, detect and treat TB in line with the “Global Plan to Stop TB” [2, 3]. Furthermore, the “Interim Policy on collaborative TB/HIV activities” [4], starting from the principle “Two diseases, one patient”, set out simultaneous patient-focused care delivery, and emphasized the necessity of implementing collaborative activities in addition to existing global strategies. However, despite this commonly agreed clear policy guidance and understanding of the need for concerted action at the international as well as at the national level, key challenges remain [5]. In addition, an integrated response to the co-epidemic has yet to be realized and joint HIV/MTB activities are severely under-funded.

The EUCO-Net core consortium convened a panel of 60 experts to generate this roadmap that identifies global research needs in the field of AIDS and TB, and HIV/MTB co-infection. The expert team included representatives of scientists, health care professionals, policymakers, activists and people living with HIV/TB. Although considered of high importance, the EUCO-Net group has not developed any recommendations for development of vaccines and new drugs since these areas have been receiving by far the most funding throughout FP6 and the first three years of FP7 [6] or been part of the recent FP7 calls (see supplementary document on AIDS/TB funding by C. Giehl). The proposed priority areas for joint AIDS/TB research and concerted actions below are divided into basic sciences, clinical research, diagnostics as well as training and networking.

PROPOSAL OF TOPICS FOR JOINT AIDS/TB RESEARCH AND CONCERTED ACTION

Basic Sciences

Since the first description of HIV in 1983 as the causative agent of the acquired immunodeficiency syndrome, there has been an impressive progress in the understanding of HIV biology, its interaction with the infected host and a concomitant extension of therapy options. This was possible due to existing funding, which in turn was made available at least in part by strong activist groups that have forced societies to booster their research activities in this area. The same does not hold for TB. With the BCG vaccine available that at least prevents disseminated TB and TB meningitis in children, and the possibility to cure TB with antibiotic treatment, TB research has been marginal for decades. As a consequence, sensitive diagnostic tests and therapeutic drugs against HIV and TB are of tremendously uneven availability today. Given the rise of TB due to the HIV pandemic and the limited options to manage MDR- and XDR-TB, there are strong accumulated needs to improve (i) the mechanistic understanding of TB pathogenesis especially in the context of an HIV infection, (ii) the therapy options and procedures for their implementation, and (iii) the diagnostic tests predictive for latent infection and active disease.

Two topics in basic science were identified that deserve further attention by concerted research activities and to which European scientists can substantially contribute. Topic 1 (see column) aims to understand in greater detail the HIV/MTB interactions within an infected host that lead to enhanced disease progression. A key element here is the formation of MTB-induced granuloma, its role in MTB containment, latency and release [7, 8]. How are these individual functions regulated and how influenced by HIV and the antiviral immune response? A consortium comprising of clinicians, pathologists, immunologists, microbiologists and virologists with access to up-to-date life imaging tools and relevant animal models could have a substantial impact on dissecting the cellular events that are at the heart of the disease. Besides the increase in basic knowledge, novel therapeutic strategies on how to contain MTB in latency or how to eliminate MTB kept latent are likely benefits from such a basic research approach.

Topic 2 continues along the significant progress made in understanding the development of HIV drug resistance [9, 10]. It aims to transfer this progress to the TB world and to combine it with TB-specific problems of drug resistance. Within the bacterial world, MTB seems unusual as it acquires much of its drug resistance by genetic mutations within the bacterial genome while for other bacteria, plasmid exchange is more common. In this respect MTB behaves like viruses for which drug resistance is associated with the outgrowth of respective virus mutants. Interestingly, it was first recognized in TB treatment that combination therapies are more successful than monotherapies to obtain long term clinical benefits [11-14]. Today the combination of drugs targeting different functions of the same virus is common practise.

The idea behind Topic 2 is simple: by understanding drug resistance pathways, defining microbial costs associated with resistance, considering immune and nutritional status, and incorporating the knowledge on drug functions and interactions, one should be able predict optimal therapy strategies especially when the first line drugs are failing. A consortium incorporating clinicians, basic researchers, drug designers and bioinformaticians should be able to significantly improve HIV/MTB management and help to reduce the frightening burden of multi-drug resistance worldwide.

**Topic 1: Understanding MTB pathogenesis in HIV infected individuals by identification of microbial virulence and host factors**

**Aim:** The aim is to understand both microbial and host mechanisms that contribute to different dynamics and clinical phenotypes of HIV/MTB co-infection. This will be achieved through highly standardized cohort studies, and the development and use of pre-clinical model systems (cell based or animal models).

**Expected Impact:** Main goals should include prediction of TB disease progression across different stages of the HIV related disease. Specifically, the precise knowledge on the pathogen interaction at the molecular and cellular level in the context of HIV/MTB co-infection and disease will contribute to the identification of new potential therapeutic targets.

**Justification:** HIV/MTB co-infection and the mutual interaction of the two pathogens is complex and poorly understood.

**Topic 2: Individualized treatment approach for TB and HIV positive individuals based on drug resistance and therapeutic drug monitoring**

**Aim:** The aim is to optimally tailor treatment in HIV/MTB co-infected patients through therapeutic drug monitoring and the development of
algorithms that predict microbial drug resistance. Based on the substantial knowledge on genotype, phenotype and clinical resistance in the context of HIV, a similar strategy will be developed for infection with MTB. Main goals should include the identification of new drug resistance markers, mechanisms of drug resistance and evolution of microbial fitness. Systematic sample collection for host genetic analysis should also be performed.

**Expected Impact:** This will lead to an individualization of treatment as well as prevention of therapy failure and spread of drug resistant HIV/MTB variants.

**Justification:** Prediction of treatment efficacy, treatment success and therapy failure is not possible.

Clinical Sciences

The interplay between the two epidemics is clearly illustrated by the situation in the sub-Saharan region of Africa, which harbours 79% of all HIV/MTB co-infected individuals [15]. Among other regions such as Russia, India, or South America, the Southern African countries are particularly hard hit as is documented by a rate of TB in excess of 2.000 per 100.000 population in a Cape Town (South Africa) informal settlement, which is largely driven by the high prevalence of undiagnosed TB [16]. Current WHO endorsed strategies, including the directly observed therapy-short course (DOTS) are clearly not sufficient to control the HIV and TB epidemic, although failed implementation of these measures could also be to blame [17].

While the risk of TB during the HIV sero-conversion period seems unaltered, this risk raises three fold in the first two years after sero-conversion [17] and there is an increased risk of recurrent TB [18], especially as the CD4 counts decline. Molecular epidemiological data demonstrated that most recurrent episodes may be the result of *exogenous* re-infections rather than reactivation of latent infection in HIV-uninfected [19] and in HIV-infected patients [18].

Multiple studies have shown a substantial survival benefit from antiretroviral therapy but active TB still occurs commonly before the diagnosis of HIV infection [20]. Many patients die of TB shortly after the initiation of antiretroviral therapy [21], there are numerous drug interactions between anti-tuberculous and antiretroviral drugs [22] and the pharmacokinetics of the drugs in adults and particularly in children are incompletely understood [23].

The effect of HIV on MDR and XDR-TB is of concern as both HIV and TB treatment success rates, the lack of infection control measures in resource-poor settings, inadequate drug-sensitivity testing and implementation of MDR-TB treatment programs could combine to lead to a MDR-TB and XDR-TB epidemic of unmatched scale [24]. The key challenges in this research area are summarised in Topics 3-6.
The diagnosis and management of TB in HIV/MTB co-infected children is another major challenge [36-39]. In the year 2000, around 11% of the global TB cases were estimated to occur in children. The highest incidence was observed in sub-Saharan Africa where it is fuelled by the HIV epidemic. While HIV-infected children have an increased risk to develop active TB after MTB exposure, they rarely develop sputum smear-positive TB and the standard tuberculin skin test to diagnose the infection is of low sensitivity [38]. Symptom-based diagnostic approaches are also of little help because differential diagnosis with respect to other HIV-related or general paediatric clinical conditions is difficult.

To address these key research challenges in diagnostics, Topics 7-10 were designed. This need complies with Rio Communities’ Declaration at the 3rd Stop TB Partners Forum (March 2009) as well as with the outcomes of the conference on “Challenges for the future: research on HIV/AIDS, Malaria and Tuberculosis” which the EC convened in Brussels in November 2008 to update the European research priorities in the field [6]. The development of new diagnostic tools that can provide faster and more accurate TB diagnosis for smear positive, smear negative and drug resistant TB, including diagnostics appropriate for children has been defined as an urgent need and should therefore be a clear priority in future research.

### Diagnostics

Because TB is a treatable disease in principle, and HIV progression can largely be slowed down by antiretroviral drugs, rapid and efficient diagnosis of both infections is of prime importance in health care. With respect to HIV infection, very sensitive and specific diagnostic assays are available. They rely on the detection of specific antibodies, measurements of viral load and CD4 T-cell counts. Tests for early TB-related mortality due to TB in HIV-infected individuals in countries of high TB incidence and will increase therapeutic options.

**Expected impact:** An increased knowledge on the effect of early ART will lead to a reduction in early mortality due to TB in HIV-infected individuals in countries of high TB incidence and will increase therapeutic options.

**Justification:** TB is currently the leading cause of death among infectious diseases in HIV-infected individuals worldwide. The TB-related mortality is excessively high in the first months following the initiation of ART. In this period, TB-related IRIS is significantly contributing to morbidity and mortality of HIV-seropositive individuals.

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<th>Topic 7: Diagnosis of latent MTB infection in HIV-infected patients</th>
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<td><strong>Aim:</strong> The aim is to correctly identify patients latently infected with MTB, to predict their risk of progression, and to rule out active TB in both HIV-infected adult and paediatric patients. Key biomarkers should be identified, validated and implemented to be used in a clinical setting.</td>
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<td><strong>Expected Impact:</strong> This monitoring technology should facilitate rapid targeting of chemoprophylaxis and therapy, and will enable to quantify the risk for progression and treatment success.</td>
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<td><strong>Justification:</strong> In HIV infection, latent TB can rapidly progress to active disease. The currently available tests are not appropriate for HIV-infected patients in high burden settings and fail to affect patient care.</td>
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<th>Topic 8: Diagnosis of active TB in HIV-infected patients</th>
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<td><strong>Aim:</strong> The aim is to develop and validate improved rapid screening technologies for active TB in both HIV-infected adult and paediatric patients that are appropriate for use in TB-endemic countries and poor resource settings. Those tests could be based on a variety of biological samples.</td>
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<td><strong>Expected Impact:</strong> This should lead to an improved case finding, better treatment outcomes, reduced transmission, and better targeting of preventive therapy.</td>
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<td><strong>Justification:</strong> TB is a leading cause of death in patients infected with HIV. Current diagnostic tools miss more than 50% of TB cases in HIV-infected individuals.</td>
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<th>Topic 9: Diagnosis of drug resistance in HIV-infected patients</th>
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<td><strong>Aim:</strong> The aim is to develop and validate improved screening technologies to assess resistance to HIV and TB drugs in both HIV-infected adult and paediatric patients.</td>
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<td><strong>Expected Impact:</strong> This should lead to prediction of treatment failure and quantitation of treatment efficacy. This will reduce transmission and improve patient care. Knowledge on drug resistance patterns will also inform infection control policies.</td>
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<td><strong>Justification:</strong> Drug resistance is an increasingly recognised problem in HIV-infected patients. We need to know the prevalence of resistance patterns in order to plan the subsequent therapeutic options in HIV/MTB co-infected patients.</td>
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Training and Networking

The “cursed duet” of AIDS/TB continues to have a dramatic epidemiologic impact in settings at high HIV and MTB burden, with potentialities for further worsening where MDR- and XDR-TB are present [3, 40], e.g. in several countries of the former Soviet Union that are the gate to Europe. Although excellent documents have been designed by the WHO and their partners (2,4-6) from both the HIV/AIDS and TB side, much still needs to be done to transform these principles into programmatic action. The principle “Two diseases, one patient”, presently representing the “politically correct” vision of the two interlinked pandemics is far from being implemented into practice. At the programmatic level, within Ministries of Health of the priority countries, the national TB and HIV/AIDS programmes have problems to transform formal contacts into effective collaboration. Funding is still a matter of competition and non-equity. At the scientific level, HIV/AIDS and TB communities are largely separate, including their meetings and conferences. Moreover, they do not yet speak the same language. Just as an example, while the TB community prefers using the term Treatment of Latent Tuberculosis Infection (TLTBI), the HIV/AIDS one uses the term Isoniazid Preventive Therapy (IPT) to mention the same intervention. At the clinical level, important gaps still exist in the two communities to manage the “other” disease affecting the “one patient”.

A major investment in training and networking is necessary at all levels (programmatic, scientific, clinical, political as well as social, psychological, etc.). if we want the “politically correct” principles are really transformed into action and the “one patient” can, at end, increase his/her chances of survival, and, hopefully, of cure. The key challenges are summarized in Topics 11-13.

Topic 10: Diagnosis of active TB in children in the context of HIV
Aim: The aim is to develop and validate new approaches that identify active TB in the context of HIV in children.
Expected Impact: This should lead to the adequate treatment of TB in children and to the prevention of TB/HIV-related childhood death.
Justification: Children are a neglected and vulnerable population often not included in TB studies. The lack of microbiological confirmation and the different clinical presentation of TB in children as compared to adults require innovative diagnostic approaches.

Topic 11: Training for translational research on HIV/TB
Aim: In order to bridge the gaps between HIV and TB communities in the EU and the different high-burden regions, a comprehensive modular training approach is needed, targeted at clinicians, public health practitioners, researchers (incl. social researchers), patient community, policy makers, laboratory personnel, civil society groups, the media, and others.
The modules should be developed using established means including task analysis, training needs, etc in order to be able to address the different needs of the target groups mentioned above, and should be easily applicable in different target regions.
Expected Impact: To reach commonly agreed guidelines, identify best practices in HIV and TB management and prevention in different settings, improve management of HIV/MTB co-infected patients, improve planning, implementation, and monitoring and evaluation of HIV/MTB co-infection programmes, and create a common base for enhanced collaborative research efforts.
Justification: HIV/MTB co-infection is a global problem; however, lack of human resources knowledgeable in both fields is a recognized weakness limiting effectiveness of existing strategies. To date only a few initiatives address these inter disciplinary training needs. This project is expected to improve the availability of a sufficient number of competent human resources for health research and management, thus contributing to better access to essential health care and achieving the health-related WHO Millennium Development Goals.

Topic 12: European TB Network of Excellence
Aim: While several HIV Networks of Excellence (NoE) are in place already, at the moment, no European TB NoE is being funded by the EC. Support shall be given to a solid and inclusive research network on TB. Main goals of a Pan-European TB Network should include improving diagnosis and prognosis of patients infected with MTB (including drug-resistant TB strains), understanding mechanisms of latent MTB infection, monitoring of treatment success, advancing understanding of pathogenesis of the infection, and proposing new interventions for infection control. The Network should be able to efficiently coordinate multi-disciplinary efforts to improve diagnosis and treatment of TB infection in Europe, both in adults and children. The inclusion of HIV co-infection issues will be considered as an asset, and should be closely coordinated with existing NoEs in the area of HIV research. The proposed NoE should provide a rationally organised joint programme of action to implement common research goals and strategies on research platforms, infrastructures and technologies, as well as standardised methods and protocols. Integration activities will furthermore comprise joint multidisciplinary training schemes and a concrete dissemination plan. Active participation of SMEs and/or Product Development Public-Private Partnership organisations could lead to an increased impact of the research proposed.
Expected Impact: This Network of Excellence will integrate and valorize ongoing TB initiatives in Europe and help create a durable joint structure to promote stronger institutional integration between core partners of the network, with the aim of structuring and strengthening the European Research Area in the field.
Justification: While several HIV NoEs are in place already, at the moment, no European TB NoE is being funded by the EC. In recent years, European TB research has successfully started to self-organize, and valuable networks have been created. These activities should be integrated to allow for concerted action and enable the creation of durable structures.

Topic 13: Global HIV/TB network
Aim: The aim is to provide long-term sustainable interaction and coordination of efforts addressing HIV/MTB co-infection. This will be achieved by detailed mapping of current networks of HIV, TB, and HIV/MTB co-infection (what is there, what is lacking, how to synergize existing initiatives). Activities should include the establishment of a joint repository of knowledge, the creation of decision making models to aid national policy makers, the promotion of infection control measures for HIV and MTB infections, monitoring the implementation of existing HIV and TB guidelines, the implementation of a guideline quality control system, and assurance of fast integration of new developments into existing guidelines. A process to engage key stakeholders in consensus building should be established. Sustainable networking with research partners and other stakeholders in disease-endemic countries should be an essential part of the project, providing a sound basis for integrated global research efforts across disciplines and diseases. Child health and ageing aspects should be taken into consideration wherever appropriate. Target regions should include Africa, India, Latin America, Russia, and SE Asia.
Expected Impact: This global NoE will integrate HIV and TB research in Europe, and connect the EU scientific community with all major endemic regions as well as leading global initiatives. It will build capacities and create a common knowledge base for coordinated action. A wide range of stakeholders, including especially patient organisations, should be represented.
Justification: Final Report on Challenges for the Future meeting (Brussels, Nov 2008) is advocating networking and mutual opening up of research groups, as well asstreamlining data collection.
CONCLUSIONS

A number of topics for future EU calls were defined by an international team of HIV/TB experts which may help guiding decisions by the EU and other funding bodies. By funding EU-CO-Net, the EU underlines their commitment in supporting the global health challenge posed by HIV/MTB co-infection. From the participants' side, the collaborative effort was a highly efficient and successful experience, demonstrating that the integration of experts with different scientific and cultural backgrounds can indeed lead to significant synergies. Solid interactions were already established and strengthened during the project’s lifetime and complementarities among partners will facilitate future collaborative activities in the area of HIV/MTB co-infection.

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