EDCTP

The power of sharing science

Co-infections and co-morbidities

EDCTP Stakeholder meeting

The Hague, the Netherlands, 13 September 2017

Report

Supported by the European Union

EDCTP - Who we are, vision, and mission

The European & Developing Countries Clinical Trials Partnership (EDCTP) is a public–public partnership funding collaborative clinical research on medicinal products to fight poverty-related infectious diseases affecting sub-Saharan Africa.

EDCTP's vision is to reduce the individual, social and economic burden of these diseases by supporting the clinical development of accessible, suitable and affordable medical interventions.

EDCTP's mission is to accelerate – while enhancing African clinical research capacity – the development of new or improved medicinal products for the identification, treatment and prevention of infectious diseases, including emerging and re-emerging diseases, through pre- and post-registration clinical studies, with emphasis on phase II and III clinical trials.

Table of contents

1 Executive summary

Co-infections and co-morbidities in low- and middle-income countries

Co-infections and co-morbidities represent an important public health problem in many areas, decreasing chances of recovery or cure and ultimately resulting in increased morbidity and mortality. Co-infections present unique challenges in diagnosis, treatment and prevention, including increased toxicity and/or decreased efficacy of interventions. Non-communicable diseases (NCDs) have become a fast-growing burden of disease in sub-Saharan Africa. Combined with the persistence of infectious disease, there is a clear need for long-term, more integrated management of poverty-related infectious diseases (PRDs) and NCDs. Co-infections and co-morbidities are among the priority topics for EDCTP to be addressed in 2018.

Meeting

The EDCTP Stakeholder meeting on co-infections and co-morbidities was held in The Hague, The Netherlands, on 13 September 2017. Participation in the meeting was by invitation. Participants included 52 representatives from academic and research institutions, funding agencies, product development partnerships, industry and international organisations, including members of EDCTP's Scientific Advisory Committee.

Dr Michael Makanga, EDCTP Executive Director, reminded the participants that the aim was to have clear recommendations from the meeting. To this end, he asked the participants to focus on top priorities for EDCTP which were realistically implementable bearing in mind the scope and focus of the EDCTP programme.

Following the welcome and opening remarks and an overview of the European Commission's investment in co-infections and co-morbidities, Professor Shabir Madhi presented the keynote address on the role of co-infections and co-morbidities in childhood, neonatal and stillbirth deaths.

The day's proceedings were then divided into four sessions, which considered co-infections and co-morbidities under the following topics:

- Challenges and perspectives in the clinical management of co-infections
- Co-morbidities associated with PRDs and NCDs and their treatments
- Tools for diagnosis of co-infections and co-morbidities
- Development and testing of products used for treatment and prevention.

The meeting closed with the chairpersons summing up the main points and recommendations from the participants.

Outcomes

The following were the key recommendations resulting from the meeting:

Assessing the burden

- A better understanding of the epidemiological burden of disease is needed. Reporting of cause of death in LMICs is incomplete, of poor quality and delayed. Minimally-invasive tissue sampling (MITS) may be an important tool in estimating disease burden.
- Integration and consolidation of diagnostic services using multi-disease platforms can bring system efficiencies, cost savings and improved quality of care.
- There is a need for simple diagnostic algorithms that can be used with little training and in the absence of rapid diagnostic tests.

Clinical management

- *Leishmania*–HIV co-infection: there is an urgent need for new drugs for visceral leishmaniasis (VL). The available drugs have had variable efficacy and serious toxicity has been reported to occur.
- HIV and Buruli ulcer co-infection: co-infected patients are difficult to cure, require long hospitalisation, and have higher risk of mortality. Lesions are more severe in HIV-immunosuppressed patients. Clinical challenges range from drug interactions in anti-Buruli ulcer therapy, to timing of ART treatment.
- For HIV and female genital schistosomiasis (FGS) co-infection, the priorities are to determine the impact of FGS on the HIV epidemic and especially in HIV-infected African women; to evaluate the efficacy of treatments of FGS lesions in HIV infection; and to integrate screening and treatment of FGS in cervical screening and HIV programmes. Additionally, point-of-care diagnostics for FGS, as well as training of health care professionals in FGS diagnosis, need improvement.
- In the case of tuberculosis (TB) and diabetes co-morbidity, patients with a diabetes condition are more vulnerable to infections. People with diabetes are three times more likely to contract TB, with 15% of all TB being ascribed to diabetes. Diabetics are at higher risk of resistance to TB medication and of drug-drug interaction.

Research and development of medicinal products for prevention and treatment

- There is a need to invest in research and development for HIV–TB vaccination. Challenges are to reach adults with vaccination programmes; conduct vaccine safety trials in co-infected populations; investigate existing interventions and vaccines for a potential impact on other diseases.
- It is important to study drug interactions with co-administration of ART and antimalarial drugs.

Repurposing

- New as well as existing drugs should be investigated for new applications, including host-directed therapies and immunomodulators.
- Off-label use of existing vaccines against infectious diseases could bring positive results within relatively easy reach ("low-hanging fruit").

Health care delivery

- There is a need for a programme to document drug–drug interaction in order that pharmacovigilance-based assessment informs guidelines.
- At a political and structural level, the need to address health care delivery was highlighted. Better integration of health care is needed to address co-infections and co-morbidities. Public and private organisations need to study the possibilities to reorganise health care services into more horizontal/diagonal care systems instead of continuing to work in separate vertical, disease-specific silos. This also needs coordination and planning at the political level.
- Multi-disease prevention needs to be prioritised and approaches from successful prevention programmes need to be adopted more broadly.
- Currently, regulatory approval and validation processes are causing often market launch delays.
- It has to be taken into account that the key HIV patient population is aging and also faces higher rates of comorbidities.

Way forward

The EDCTP Scientific Advisory Committee meeting will discuss the recommendations from the meeting with the aim to further refine them. The intention is to take forward some of the recommendations and included these in EDCTP's strategic research agenda for 2018. EDCTP aims to have a call in this important area in 2018.

2 Introduction

The Stakeholder meeting on co-infections and co-morbidities was opened by EDCTP's Executive Director **Dr Michael Makanga**. He put the meeting in context by referring to the broad priorities outlined in EDCTP's strategic business plan, and stating that they form the basis of more specific three-year plans. These three-year plans are developed in consultation with EDCTP's Scientific Advisory Committee, taking into consideration the current EDCTP portfolio and the input from thematic EDCTP Stakeholder meetings. EDCTP is currently in the process of planning the priorities and scope for the three-year plan for 2018–2020.

Co-infections and co-morbidities are among the priority topics to be addressed in 2018. It is therefore crucial to be well-informed on the research priorities in this area. Outlining the purpose of the Stakeholder meeting, he said it is important to hear what others are doing in the area and to receive this valuable input from the invited stakeholders. The outcome of the meeting will inform annual strategies and help in the process of establishing 2018–2020 priorities.

Regarding the topic of the meeting, he said that many pathogens are involved. In the process of prioritising, it is important to identify areas EDCTP could address either by itself or in partnership with others, as well as areas that it could leave to others. The recommendations from the Stakeholder meeting will inform the discussions of EDCTP's Scientific Advisory Committee.

Dr Ole Olesen (EDCTP Director of North-North Cooperation) gave a background to EDCTP, whose scope covers HIV, tuberculosis (TB), malaria, neglected infectious diseases (NIDs), diarrhoeal infections, and lower respiratory infections as well as emerging or re-emerging infectious diseases. He described EDCTP's unique partnership structure, i.e. an equal public–public partnership between African and European governments: 15 African and 14 European member countries with additionally Switzerland as an aspirant member[1]. The activities of EDCTP are, however, not restricted to these member countries.

Dr Olesen informed participants of EDCTP's approach to health research: its strong focus on collaboration at all levels (between funders as well as research teams from Europe and Africa); extensive research networking including; support of strengthening the regulatory and ethical environment in Africa; and reaching out to policy makers. The aim of the meeting, he said in conclusion, was to maintain momentum and stay at the forefront of scientific trends. For the most relevant science to be applied to benefit sub-Saharan African countries, input in the form of participants' priorities was needed from the meeting.

Dr Alessandra Martini (European Commission) provided an overview of the 'European Commission's investment in the area of co-infections and co-morbidities' and a background to European Union co-funding of EDCTP via the Horizon 2020 programme. She said that co-infections and co-morbidities are recognised as an important global public health problem with many diagnostic, prevention and treatment challenges. She listed several European Union-supported projects conducted in this important research area, funded under Framework Programme 7 (FP7)-Health, such as the COBRA study on HIV-related accelerated ageing and the TANDEM study on the causal relationship between tuberculosis and diabetes mellitus.

In light of the many research gaps and needs, prioritisation is paramount. She stressed the importance to the European Commission of consultative meetings, such as this Stakeholder meeting, at which priority areas could be identified. Co-infection and co-morbidities are included in the proposals and planning of the scientific work programme for 2018–2020 and, after 2020, the new Framework Programme FP9 for which discussions and preparations have already begun.

Meeting chairs, meeting objectives and expected outcomes

Dr Makanga introduced the chairs of the meeting, **Dr Maryline Bonnet** (Institute of Research for Development, France) and **Professor John Gyapong** (University of Health and Allied Sciences, Ghana), both members of the EDCTP Scientific Advisory Committee.
Prof. Gyapong recapitulated the meeting's four key objectives:

1: to review the research landscape, including the key clinical research questions and barriers to progress in sub-Saharan Africa;
2: to discuss the available interventions and products in development with the major partners working in this field;
3: to reach out to stakeholders involved in this field to collaborate with in the execution of future EDCTP activities; and
4: to identify priority areas for EDCTP in terms of disease, research and intervention priorities in this field, both in the short and in the medium term.

[1] *As of December 2017, the number of African member countries changed to 16 with Ethiopia joining the EDCTP Association. Angola joined as an aspirant member.*

He stressed the importance of setting priorities. The goal was not to end up with a "wish list" of research interest desires, but to formulate clear goals on what EDCTP should work on in the medium term, and how to arrive at those, by looking at what is already available in the landscape. The focus should be on the most important areas where EDCTP could make an impact, and on opportunities for adding value to interventions already in place. Dr Bonnet added that in prioritising within this very large landscape, EDCTP's framework and approach should be kept in mind.

Keynote address: *Unravelling the role of co-infections and co-morbidities in childhood, neonatal and stillbirth deaths: role of minimal invasive tissue sampling in resetting our focus*

The keynote address was delivered by **Shabir A. Madhi** (National Institute for Communicable Diseases and University of Witwatersrand, South Africa), who said that we are currently at a critical juncture in terms of our ability to determine the role of co-infections and co-morbidities. While health priorities need to be based on informed decision-making, for many countries we do not know the cause of death among under-fives and stillborn children. The contribution of different co-infections and co-morbidities is unclear. Global burden of disease and mortality figures are based on estimates, with an almost total absence of hard information. Verbal autopsy, which remains the primary means of determining cause of death in high-mortality areas, is unspecific, providing little more than an epidemiological "snapshot". Excluding China, India and Latin America, more than half of the low- and middle-income countries (LMICs) have no cause of death information available and only five LMICs provide national verbal autopsy data on cause of death. At best, therefore, our understanding of under-five mortality in the world's countries with high mortality is based on verbal autopsy in a handful of countries.

Moreover, it is difficult to relate the cause of death to a specific infection when several pathogens are identified. When a single disease is identified as the underlying cause of death – in line with WHO certification recommendations – it means that the immediate cause of death is often unrecognised, as is any co-morbidity. With actual incidence data lacking, it is not possible to develop relevant pathogen-specific mortality models. In addition, the time lag between data collection and the development and implementation of the models means that interventions are based on past data.

In response to the need for better tools, the Child Health and Mortality Prevention Surveillance (CHAMPS) network, with funding from the Gates Foundation, has developed an easy-to-use minimally invasive tissue sampling (MITS) kit. The kit allows obtaining specimens from the vital organs and bone marrow, as well as blood, cerebrospinal fluid and stools, in a manner more culturally acceptable than autopsy. One study investigating attribution of cause of death among under-fives has reported similar results for complete diagnostic autopsy and for MITS. To date, six CHAMPS surveillance sites have been established; other funders are needed to expand the MITS programme.

Discussion

Dr Bonnet asked **Prof. Madhi** what role he saw for EDCTP in regard to the need for a better understanding of the role of co-infections and co-morbidities. Prof. Madhi responded that, in order to make a global impact, the MITS programme needs to be expanded to 20–25 countries and to adults as well. Such an expansion would exceed the capabilities of a single funder. EDCTP, through its partnership approach, could potentially be involved as a funder. Responding to a pricing-related question, he said the pilot studies had cost approx. US$3,000 per case but it is hoped that local ownership and regional hubs will bring costs down. One participant highlighted the need to expand the MITS tool to cover maternal deaths, and that there could be a role for EDCTP in this area. (Later in the day, it was highlighted that cheaper diagnostics are needed and the suggestion was made that EDCTP might provide funding for product-focused implementation research in sub-Saharan Africa focusing on low-cost diagnostics with proven efficacy.)

One question was related to the cultural sensitivity of performing autopsies. (Speaker's answer: The MITS approach is more acceptable than autopsy; however, community engagement is an important aspect of the success of MITS. In this context, one participant noted that there is a need for social science research on how to use interventions in a way that is appropriate for a specific population.) Another question raised was the acceptable time lag between time of death and sampling. (Answer: Twenty-four hours or less after death). One participant enquired about the ability of MITS to identify non-infectious co-morbidities, for example organ damage. (Answer: The specificity of MITS is improved when combined with clinical information.) Another concern mentioned was antimicrobial resistance. (Answer: In the original MITS study, a number of children had died in the community, and the disease profile in the community had differed from that in health facilities. Therefore, it is vital to include information on children who die in the community.)

One participant asked how to use this information in locations with limited access to diagnostic tools, adding that the training of pathologists is a long-term effort. (Answer: Local capacity will eventually need to be developed; for now, central labs are available, making real-time data accessible even to resource-limited settings. The CHAMPS programme has already triggered shifts in approaches to nosocomial infection and stillbirths, etc.)

A comment that was raised, both during this discussion and later in the day, was that in the presence of so many pathogens, it is not possible to eradicate them one by one by pathogen-specific interventions.

In summary

Cause of death data in LMICs are incomplete, of poor quality and delayed. They provide very little insight into the role of co-infection and co-morbidity in child mortality. Better information and tools are needed to inform priority setting. Cause of death data from children, including those dying at home, as well as stillborn children, are needed to support priority setting internationally and locally; hard data are needed for government health planning, especially in low-resource settings. In order to make a global impact, the MITS programme needs to be expanded to 20–25 countries and to adults as well.

3 Challenges and perspectives in the clinical management of co-infections

The first presentation on clinical management of co-infections dealt with Leishmania–HIV co-infection. **Dr Jorge Alvar** (Drugs for Neglected Diseases initiative, Switzerland) described an urgent need for new drugs for visceral leishmaniasis (VL). The available drugs have had variable efficacy. Only one (miltefosine) is administered orally. Serious toxicity has been reported to occur especially in VL–HIV patients. Early relapse is common.

Pathogenically, HIV and leishmaniasis can co-occur in the same person and same cell. HIV may abrogate effective immune responses during natural infection and reactivate VL in previously asymptomatic Leishmania carriers. In co-infected patients, Leishmania has been reported to hasten HIV progression. Before HAART (highly active antiretroviral therapy), one in five co-infected patients had died during the first VL attack; 60% with clinical cure had relapsed; and survival had been short (11–13 months after effective treatment). HAART has decreased the incidence of new VL cases, affected the relapse pattern, and increased the survival of co-infected patients. However, VL negatively affects immunological recovery despite HAART. In light of toxicity concerns, the question is when to initiate secondary prophylaxis to prevent VL relapse in HIV-infected patients.

The LEAP study in Ethiopian VL–HIV-co-infected patients, evaluating the efficacy of AmBisome® monotherapy versus AmBisome in combination with miltefosine, showed results in favour of the combination arm on follow-up days 29 and 390. It also reported increased efficacy with extended treatment (58 days versus 29). Despite these somewhat promising results, concluded Dr Alvar, existing drugs have reached their full potential and new, safer drugs are urgently needed.

Presenting the case of HIV-Buruli ulcer (BU) co-infection, **Dr Vanessa Christinet** (Centre International de Recherches, d'Enseignements et de Soins (CIRES), Cameroon) reported higher HIV prevalence among BU- versus non-BU-infected individuals. Co-infected patients are difficult to cure, require long hospitalisation, and have higher risk of mortality. Lesions are more severe in HIV-immunosuppressed patients.

Clinical challenges range from drug interactions in anti-BU therapy, to timing of ART treatment.

In relation to HIV-infected women co-infected with female genital schistosomiasis (FGS), **Dr Christinet** reported that trends for FGS in sub-Saharan Africa are a cause for concern, and that more epidemiological studies are urgently needed.

There is a high overlap between HIV and FGS and an increased risk of HIV infection in FGS patients, with chronic FGS lesions in the genital mucosa providing an entry point for HIV. Young FGS-infected girls in sub-Saharan Africa are highly vulnerable to HIV infection once they become sexually active. Given the prevalence of HIV in sub-Saharan Africa and the trend to record the primary infection, further studies on FGS as a causal factor are of interest. Among the treatment challenges are difficulty to diagnose FGS, whose symptoms are non-specific and include vaginal itching, burning, bleeding and vulvar lesions. There is no effective way to treat and prevent recurrent lesions due to recurrent infections, and the rate of re-infection is extremely high in these populations.

Priorities are:

- to determine the impact of FGS on the HIV epidemic;
- to determine the impact of FGS in HIV-infected African women;
- to evaluate the efficacy of treatments of FGS lesions in HIV infection;
- to integrate screening and treatment of FGS in cervical screening and HIV programmes.

Additionally, point-of-care diagnostics for FGS, as well as training of health care professionals in FGS diagnosis, need improvement.

Discussion

The panellists were **Dr Victor Mwapasa** (University of Malawi) and **Dr Dawit Wolday** (Mekelle University College of Health Science, Ethiopia). Referring to the large number of people in endemic areas who were on ART, Dr Mwapasa said that in some countries, patients with access problems may attempt treatment using home-based remedies. This constitutes unsupervised treatment that requires pharmacovigilance evaluation.

The clinical challenge described by Dr Wolday particularly captured the attention of the audience and was to re-emerge later in the day's discussions: how to define a normal, healthy control in a sub-Saharan African setting? "Apparently healthy" African adults have much lower CD4 counts than other populations. As most reference values are based on Caucasian populations, defining normal reference ranges for sub-Saharan Africa is a challenge to be addressed in clinical trials. (Comment - One participant noted the need to take other values besides CD4 counts into account.)

Dr Wolday further reminded the meeting that "co-infections" often means multi-infections involving many pathogens, with implications for both diagnosis and disease management. It was commented that in the African clinical setting, diagnosis can be challenging. There are no point-of-care tools to test for multi-infection.

Referring to the discussion on the need for African reference values, one participant observed that therapies also are based on Caucasian populations – populations not affected by factors such as malnutrition. Furthermore, within Africa, ethnic diversity in drug response is huge: there is no such thing as "one African population". Moreover, combination therapies which are essential for co-infections, can lead to drug-related adverse events and adherence problems. (Comment - These issues call for pharmacokinetics and pharmacovigilance studies – especially with regard to VL treatment and ARVs.) New drugs for treatment are critical.

A further question related to interactions with HIV2. (Answer: These might exist, but the speakers were not aware of any). It was stated that the field knows very little about the interaction with HIV2. One participant commented that HIV2 is endemic only in West Africa, but given the currently slow spread of the virus it would be interesting to know whether, with co-infections and co-morbidities, it will speed up.

In summary

Regarding Leishmania–HIV co-infection, there is an urgent need for new drugs for visceral leishmaniasis. The available drugs have had variable efficacy and serious toxicity has been reported to occur.

HIV and Buruli ulcer co-infection: Co-infected patients are difficult to cure, require long hospitalisation, and have higher risk of mortality. Lesions are more severe in HIV-immunosuppressed patients. Clinical challenges range from drug interactions in anti-BU therapy, to timing of ART treatment.

For HIV-FGS co-infection the priorities are: to determine: the impact of FGS on the HIV epidemic and especially in HIV-infected African women; to evaluate the efficacy of treatments of FGS lesions in HIV infection; to integrate screening and treatment of FGS in cervical screening and HIV programmes. Additionally, point-of-care diagnostics for FGS, as well as training of health care professionals in FGS diagnosis, need improvement.

4 Co-morbidities associated with PRDs and NCDs and their treatments

Dr Rashida Ferrand (London School of Hygiene & Tropical Medicine, UK, and Biomedical Research and Training Institute, Zimbabwe) opened her presentation titled 'Changing goalposts: HIV and co-morbidities' by stating that HIV is here to stay. There is no cure yet and the disease continues to spread. Still, good progress has been made in epidemic control, meaning that today there are fewer new infections than HIV-related deaths. The burden of the disease is shifting as the HIV patient group is ageing with individuals getting infected later and surviving longer.

The changing spectrum of disease requires more investment in the epidemiology of comorbidities including NCDs. Among multiple NCDs, cardiovascular disease is a top co-morbidity. Moreover, HIV is associated with accelerated immunosenescence as well as ageing in combination with inflammation, i.e. so-called "inflammaging" due to a combination of drug, lifestyle and biomedical consequences.

The paediatric HIV epidemic has also seen a shift in the burden of disease from infants to older children/adolescents. Enormous successes have been reported for the prevention of mother-to-child transmission, but eventually children with HIV will be on ART longer than adults. ART commencement early in life leads to organ damage, as well as growth failure and puberty delay (which in turn increase the adult burden of NCDs), low bone mineral density and higher risk of fractures, stunting, cognitive impairment, hearing and vision impairment, and arthritis, affecting both quality of life and socioeconomic status.

In summary, the HIV landscape is changing and the shifting goalposts make long-term thinking imperative. Key issues include the prevention of new infections, retention in care and adherence, drug resistance in the context of lifelong treatment, economic constraints in sustaining long-term treatment, and the increased risk of co-morbidities. With the success of prevention and ARV programmes, the HIV burden is slowly shifting as the patient population ages; infants and children will now grow up to become adolescents and adults, likely being on ARVs for multiple decades. As the HIV patient population ages there will also be a rising burden of NCDs.

There will be an increasing overlap and/or concurrence of (co-) infections and comorbidities of NCDs. ART has transformed HIV into a chronic condition, with a resulting blurring of the interface between infection and NCDs.

In essence, ART is necessary but not sufficient. Important lessons have been learnt since the beginning of the epidemic, among others, that the health service approach should be "diagonalised". There is a need to start approaching interventions holistically and strengthen health systems and avoid thinking in disease 'silos'.

Between a siloed ('vertical') approach to health care (in which a clinic addresses only one disease/health problem in a patient), and, at the other extreme, a fully integrated ('horizontal') health care approach (where every clinic would treat all conditions, requiring physicians and nurses to be highly trained in many areas) the case was made for 'diagonalised' care where a clinic might be specialised in one (or several) area(s), but will also provide more comprehensive care for patients' other conditions while they are at the clinic. Services mobilised in response to HIV, including the first large-scale continuity-of-care programmes, could in this way be extended to other diseases.

Mr Ronan L'Heveder (Santé Diabète, France) gave a presentation on diabetes and TB in Africa. He said that diabetes is no longer a "developed country disease": 46.5% of people living with diabetes globally are undiagnosed and 75% live in LMICs. To put the disease in perspective, in 2015, globally 5 million adults died from diabetes, compared with 3.6 million mortalities from HIV/AIDS, tuberculosis and malaria together. (Comparison with figures from 2013, when there were 1.5 million mortalities from HIV/AIDS, 1.5 million from TB and 0.6 million from malaria).

Despite the high burden, less than 2% of health funding is spent on NCDs. Insulin is available in only 40% of countries. In Africa, 63% of diabetics are undiagnosed; and a mere 11% are receiving medication. Currently, an estimated 14 million sub-Saharan Africans are living with diabetes. This number is expected to rise to 34 million by 2040.

A major factor in this increase is urbanisation, which is associated with lack of physical activity as well as unhealthy diet, in turn leading to overweight and obesity. Education, at all levels, is paramount in combating the disease and preventive programmes are badly needed, including adaptation of existing health systems and a shift to horizontal integration of care.

Patients with a diabetes condition are more vulnerable as people with diabetes are three times more likely to contract TB, with 15% of all TB being ascribed to diabetes. Diabetics are at higher risk of resistance to TB medication and of drug-drug interaction. L'Heveder closed by outlining a three-step plan drawn up by Santé Diabète to disseminate knowledge about the disease and its prevention in West Africa, with a focus on capacity building to deal with the forthcoming diabetes epidemic.

Discussion

The panellists were **Professor Andre Pascal Kengne** (NCD Research Unit, MRC, South Africa) and **Simon Chell** (GlaxoSmithKline, UK).
Prof. Kengne opened the discussion by posing two research questions:

- How can we divert HIV resources to access and care for NCDs;
- How can we promote co-screening for and co-control of NCD co-morbidities together with HIV?

Because of the explosion of HIV in Africa, the health systems are geared towards diagnosis and treatment of infectious diseases. However, the increasing burden of NCDs necessitates a change in approach. Opportunities are missed if HIV is the primary and only, focus. As a way forward, there needs to be investment in promotion of co-prevention, co-detection, co-treatment and co-control of NCDs in Africa.

Mr Chell, addressing the topic from a pharmaceutical industry perspective, described interest in what is unique in the way NCDs manifest in sub-Saharan Africa and in the way they might respond to treatment. There is a need to consider pharmacogenetics and intraregional variations when developing treatment. There is also an increasing interest in breaking down the boundaries between what was classically called 'infectious diseases' and NCDs, and in looking at the picture as a multiple disease burden. It was noted by one of the participants that currently GlaxoSmithKline's Africa NCD Open Lab is the only laboratory offering the opportunity to conduct NCD research in Africa.

The audience agreed that the focus should not only be on HIV: the interaction between other poverty-related infectious diseases and NCDs should also be considered. However, the role of HIV in inflammation and infection is important and more epidemiological data at the individual, social, and population level on the risk factors of the HIV epidemic would be of value. Further, HIV is a good platform from which to look at other diseases. HIV has taught us a great deal about how to implement long-term health programmes and activate government focus. The success of HIV programmes should be extended to other diseases. In summary, HIV-related infrastructure should be used as a platform for NCD research and prevention; lessons learned from HIV centres can be applied to other conditions (infectious and non-infectious).

There needs to be more integration between health research and health delivery in spite of the fact that both funding and systems promote verticality, treating diseases such as HIV and TB as silos. One participant warned about the complexity of integration, saying that different health workers have different ideas about the meaning of integration. It was suggested that perhaps EDCTP could consider a partnership to work on co-morbidities addressing the integration issue. Or there might be a role for industry in helping countries to achieve integration in health care?

Returning to the problem of access to medicines, raised previously, one participant argued that access is not the only issue: for instance, new diabetes drugs are available but affordability is a problem. The need to focus on low-cost, feasible, scalable interventions when supporting implementation research was identified. Further, drug–drug interaction was highlighted as a clear policy gap that needs to be addressed.

One participant commented on the diabetes incidence figures quoted by L'Heveder, saying that for example rural and urban populations differ regarding insulin resistance. Type 1 diabetes is everywhere, while type 2 diabetes is mainly an urban disease. Dr Bonnet later noted that, in light of gestational diabetes increasing the risk of future development of type 2 diabetes, it would be of value to study the disease progression in an African setting, both looking at potential causal variables and investigating disease progression in relation to co-infections.

In summary

- The focus should not only be on HIV: the interaction between other poverty-related infectious diseases and NCDs should also be considered. However, the role of HIV in inflammation and infection is important and more epidemiological data on the risk factors of the HIV epidemic would be of value.
- The HIV patient group is ageing with individuals getting infected later and surviving longer. Key issues include the prevention of new infections, retention in care and adherence, drug resistance in the context of lifelong treatment, economic constraints in sustaining long-term treatment, and the increased risk of co-morbidities.
- The approach of the successful HIV programmes should be extended to other diseases and HIV-related infrastructure should be used as a platform for NCD research and prevention. This calls for more integration between health research and health delivery in spite of the fact that both funding and systems promote verticality, treating diseases such as HIV and TB as silos.
- The need to focus on low-cost, feasible, scalable interventions when supporting implementation research was identified. Further, drug–drug interaction was highlighted as a clear policy gap that needs to be addressed

- Patients with diabetes condition are more vulnerable to infection. People with diabetes are three times more likely to contract TB (with 15% of all TB being ascribed to diabetes), are at higher risk of resistance to TB medication and of adverse effects of drug-drug interaction.
- There is a need to consider pharmacogenetics and intraregional variations when developing treatment.

5 Tools for diagnosis of co-infections and co-morbidities

The ability to diagnose multiple, concurrent co-infections is becoming essential, was the opening statement of a talk on diagnostics, given by **Mr Philippe Jacon** (Cepheid, France). Moreover, diagnostics present new opportunities for collaboration and integration. New laboratory techniques allow for testing of different conditions using disease-specific tests on the same platform. Among the benefits of polyvalent platforms are system efficiency, cost savings, increased patient access, and improved quality of care. Another benefit is availability of results of multiple tests and immediate commencement of treatment during the same health encounter, which is important in terms of prevention of loss to follow-up. Although the tools exist, however, people can be "territorial" – standing in the way of collaboration between, for example, national TB control programmes and national HIV programmes. Vertical programmes present a significant barrier to bringing different groups together to share multi-disease diagnostic tools, which is necessary to address the challenge of co-infections and co-morbidities. Therefore, services need to be integrated and consolidated, requiring coordination in planning at a political level. At present, the speaker stated, regulatory approval and validation processes are causing huge delays.

Discussion

Panellists were **Dr Sabine Dittrich** (FIND, Switzerland) and **Dr Sébastien Quesney** (Fondation Mérieux, France). Dr Dittrich said that the presence of co-infections and co-morbidities makes testing difficult. Multi-disease tests can be difficult to interpret. There is a need to understand the epidemiology of co-infections and co-morbidities in different regions to know which multiplexing platforms are needed and where. Also, there is limited access to samples for development of new assays.

Dr Quesney pointed out that diagnostic tools in use on the African continent are imported from other continents. There is still a lack of rapid diagnostic tests in Africa, due partly to absence of market incentives and partly to product developers having limited access to samples. This could be addressed by constructing improved diagnostic algorithms and training people locally to develop rapid tests. He emphasised the need for simple diagnostics as well as molecular diagnostics.

Linking to the discussion on multi-disease diagnosis, one of the presenters of the following session, **Prof. Byakika-Kibwika**, told the audience that diagnosis in patients with HIV–TB co-infection is problematic, with increased incidence of smear-negative TB, and smear microscopy detecting <50% of HIV-associated TB. She added that the low accuracy of clinical diagnosis is likely due to atypical forms of TB. Despite successes with the lateral-flow urine TB LAM test in HIV–TB patients, diagnostic challenges contributed to treatment delays with possibly consequences such as longer disease transmission and increased mortality. The WHO-recommended diagnostic algorithms have shown poor performance. Moreover, simplified diagnostic algorithms are needed for smear-negative TB in HIV patients in low-resource African settings. Also needed are: rapid TB tests for resource-limited settings; improved diagnosis of non-TB conditions that mimic TB in HIV patients; and targeted diagnostics training of clinicians.

One participant commented on the lack of NCD diagnostics in sub-Saharan Africa – especially in the field of autoimmune diseases.

Another participant described the problems of implementing rapid diagnostic tests in the field. These are sometimes related to acceptance issues among local health personnel regarding performance of rapid tests, where the social context and status of local health professionals can come into play. It was commented that industry may play a role in supporting diagnostic training, in parallel with developing lab knowhow. A further comment concerned the importance of keeping samples and to have well-managed biobanks.

A final comment related to anaemia as a common morbidity. In malaria-endemic areas, people refuse iron supplementation for fear of increasing the risk of malaria.

In summary

- The ability to diagnose multiple, concurrent co-infections is becoming essential;
- Diagnostic challenges contribute to dangerous treatment delays; rapid diagnostics in the field still present challenges.
- Preserving samples and well-managed biobanks are important.
- Regulatory approval and validation processes are causing too many delays.

6 Development and testing of products used for treatment and prevention

Dr Gerald Voss (Tuberculosis Vaccine Initiative, the Netherlands; Global HIV Vaccine Enterprise, USA) reported on 'Vaccines to fight co-infections and co-morbidities in African countries'. He asserted that vaccines can protect against several infectious diseases together, and that they have an enormous impact. However, the vaccine development process is complex and multi-disciplinary and can take as long as 10 years from antigen identification to a phase I trial alone. For this to be sustainable there is a need for product development partnership models. Voss said that here he saw a role for EDCTP for support and collaboration at the stage of clinical development.

Moving on to prevention and treatment of HIV–TB co-infections, he said there is currently no HIV or TB vaccine with confirmed efficacy, except BCG. Hence there is a need to invest in research and development in HIV–TB vaccination. Among others, needs and challenges are to:

- reach adults with vaccination programmes;
- conduct vaccine safety trials;
- in co-infected populations, investigate existing interventions and vaccines for a potential impact on other diseases (e.g. influenza vaccines).

He continued that, in this context, he saw enormous potential for initiatives such as the recently launched African AIDS Virtual Network *(www.aavvi.net or twitter @aavvi_net)* which, through virtually connecting scientists, advocates, community leaders and global partners, aims to accelerate development of vaccine candidates for Africa by increasing African participation in HIV vaccine research and development. Regarding a role for EDCTP, he suggested it could potentially be involved in post-marketing product testing in co-infection settings. Other areas for potential partnerships are: investment in mid-stage clinical trials in co-infection settings; and capacity building in vaccine development – for instance, through developing virtual tools.

'HIV co-infections and co-morbidities' was the topic of a presentation given by **Professor Pauline Byakika-Kibwika** (Infectious Disease Institute, Makerere University, Uganda), during which she outlined the effect of HIV on malaria disease, TB, and other co-infections and co-morbidities, before examining products used in diagnostics and treatment.

She reported that prophylaxis with trimethoprim-sulfamethoxazole in combination with insecticide-treated nets has markedly decreased the incidence of malaria in HIV-infected African populations even despite resistance-conferring mutations in Africa. There is a potential for pharmacokinetic drug interactions with co-administration of ART and antimalarial drugs. As a result of these, antimalarial drug exposure may be either increased, causing enhancement of malaria treatment efficacy and post-treatment prophylaxis and/or unanticipated toxicity, or reduced, creating risk for treatment failure. More HIV–malaria drug interactions such as previously documented may be expected. She reported several drug interaction studies that had investigated co-administration of rifampicin, nevirapine, efavirenz, and LPV/r3 with DHA, artemether, lumefantrine, and artemether-lumefantrine, with varying results.

Discussion

Panellists were **Professor Christine Stabell Benn** (Staten Serum Institut, Denmark; Bandim Health Project, Guinea-Bissau) and **Professor Gary Maartens** (University of Cape Town, South Africa). Referring to drug-disease interactions, Prof. Stabell Benn said that an approach to the development of medical interventions with a focus on a solution per disease is not only costly, but also no longer appropriate. Products for treatment and prevention of multiple diseases are required. In this context, she said that vaccines like BCG have been effective in addressing many diseases. In other words, vaccines might be used to prevent other diseases beyond their original target disease.

During the day's discussion the audience heard that in young females, the smallpox vaccination has been reported to protect against HIV, one example of interventions that may have more general effects than anticipated. At that point, the hypothesis was expressed that the smallpox vaccination may protect against FGS. Another participant said that influenza vaccination in pregnant women has been seen to protect infants against lower respiratory tract infections and susceptibility to bacterial infections.

Prof. Stabell Benn reiterated a point she had made earlier, that we need to determine what constitutes a healthy immune system, and try to achieve this state. Rather than producing pathogen-specific vaccines, what is needed are interventions that strengthen the immune system.

Prof. Maartens posed the question whether it is appropriate to study a vaccine in an HIV-infected population but not in an uninfected population? On the question of prevention in TB, he said that an optimal preventive therapy in people on ART needs to be looked into. For HIV and TB vaccine development to be successful there is a need to invest in mid-stage clinical trials in co-infection settings.

Questions and comments from the participants related to Hepatitis B and C virus (HBV, HCV) as co-infections. HCV treatment is effective; more research on HBV is needed. There is as yet no cure for HBV. HBV co-infection in HIV is "incidentally" addressed within HIV programmes. One comment related to the need to further investigate bacterial co-infections. It was suggested that EDCTP should take forward work in relation to WHO's new advanced HIV disease guidelines, with major knowledge gaps including on bacterial infection in people with advanced HIV disease; the ideal package of protection; and CD4 quantitative tests.

With regard to HIV today and going beyond, the development of new tests and better access to existing tests remain a priority, and so does better characterisation of cause of death. The goal first and foremost is to save lives. HIV remains a major killer and prevention of deaths today must be a priority today.

In summary

- There is a need to invest in research and development for HIV–TB vaccination. Challenges are to reach adults with vaccination programmes; conduct vaccine safety trials in co-infected populations; investigate existing interventions and vaccines for a potential impact on other diseases.
- It is important to study drug interactions with co-administration of ART and antimalarial drugs.
- EDCTP could potentially be involved in: post-licensure product testing in co-infection settings; mid-stage clinical trials in co-infection settings; and capacity building for vaccine development (including the development of virtual tools).
- Further, it was also recommended that EDCTP would take forward work in relation to WHO's new advanced-HIV-disease guidelines, identifying major knowledge gaps including: bacterial infection in people with advanced HIV disease; the ideal package of protection; and CD4 quantitative tests.

7 Recommendations

Introducing the last session of the day, **Dr Michael Makanga** asked the participants to identify top priority areas related to co-infections and co-morbidities, taking into account antimicrobial resistance. He requested the meeting to make key recommendations in the area of malaria and NIDs in the context of co-infections and co-morbidities. Suggested priorities included vaccine clinical trials; as well as adjusted-dose antimalarial studies in a bid to counter drug resistance. Others were implementation studies and viral load monitoring in patients on long-term ART; and development of an immune-enhancing intervention to reduce antimicrobial resistance.

Summing up, **Dr Bonnet** reminded the audience of the main topics discussed during the day. In the discussion that followed, one comment from the audience pertained to the absence of certain topics from the day's discussion, for example helminth infections, leprosy, and respiratory health beyond TB. Prof. Gyapong acknowledged the in itself limited scope of a one-day meeting, but said that non-mention of certain infections did not imply that EDCTP did not consider them important. **Prof. Gyapong** then urged the audience to pinpoint priority areas that could feed into EDCTP's processes.

The recommendations of the meeting included the following:

- A better understanding of the epidemiological burden of disease is needed.
- There is a need for simple diagnostic algorithms that can be used with little training and in the absence of rapid diagnostic tests.
- New and existing drugs should be investigated for new indications, including host-directed therapies and immunomodulators.
- There is a need for a drug–drug interaction programme in which pharmacovigilance informs.
- At the political and structural level, the need to address approaches to health care delivery to better integrate management of co-infections and co-morbidities was highlighted. Public and private organisations need to study the possibilities to reorganise health care services into more 'horizontal' or 'diagonal' care systems instead continuing to work in separate vertical, disease-specific silos.
- Off-label use of existing vaccines against infectious diseases could bring positive results within relatively easy reach ("low-hanging fruit").
- Multi-disease prevention needs to be prioritised and successful prevention programmes need to be broadened.
- Against the backdrop of successful ARV programmes, it has to be taken into consideration that the key HIV patient population is an ageing population which gives rise to co-morbidity issues.

Closing remarks

Closing the stakeholder meeting, **Michael Makanga** said that a great deal had been captured during the meeting. Over the next two days EDCTP was holding its Scientific Advisory Committee meeting and the recommendations would be one of the items looked at with the aim to further refine them. The intention was to take forward some of the recommendations and have them feature in EDCTP's strategic research agenda for 2018. EDCTP was hoping that it would have a call in this important area in 2018. He added that the recommendations were not only for EDCTP's use but would also be shared with EDCTP member states and other funding partners to inform their funding strategies. Makanga thanked all present for a very rich discussion and contribution.

Annex 1: Meeting agenda

08:45-09:30	Registration & Coffee/Tea
09:30-09:50	Welcome and introduction to EDCTP Dr Michael Makanga and Dr Ole Olesen, *EDCTP, the Netherlands*
09:50-09:55	European Commission investment in the area of co-infections and co-morbidities Dr Alessandra Martini, *European Commission*
09:55-10:05	Introduction of meeting chairs, meeting objectives and expected outcomes Dr Maryline Bonnet, *Institute of Research for Development, France* Professor John Gyapong, *University of Health and Allied Science, Ghana*
10:05-10:45	Keynote address Professor Shabir Madhi National, *Institute for Communicable Diseases and University of Witwatersrand, South Africa*
10:45-11:00	Discussion
11:00-11:15	Coffee/Tea
11:15-11:30 11:30-11:45	Challenges and perspectives in the clinical management of co-infections Dr Jorge Alvar, *Drugs for Neglected Diseases Initiative (DNDi), Switzerland* Dr Vanessa Christinet, *Centre International de Recherches, d'Enseignements et de Soins (CIRES), Cameroon*
11:45-12:15	Discussion Dr Victor Mwapasa, *University of Malawi, Malawi* Dr Dawit Wolday, *Path Medical Services & Mekelle University College of Health Sciences, Ethiopia*
12:15-12:30 12:30-12:45	Co-morbidities associated with PRDs and NCDs and their treatments EDCTP Ethics and Regulatory Dr Rashida Ferrand, *London School of Hygiene & Tropical Medicine, UK; Biomedical Research & Training Institute, Zimbabwe* Mr Ronan L'Heveder, *Santé Diabète, France*
12:45-13:15	Discussion Mr Simon Chell, *GlaxoSmithKline, United Kingdom* Professor Andre Pascal Kengne, *Non-communicable Diseases Research Unit, MRC, South Africa*
13:15-14:00	Lunch
14:00-14:15	Tools for diagnosis of co-infections and co-morbidities Mr Philippe Jacon, *Cepheid, France*
14:15-14:45	Discussion Dr Sabine Dittrich, *FIND, Switzerland* Dr Sébastien Quesney, *Fondation Mérieux, France*
14:45-15:00	Development and testing of products used for treatment and prevention Dr Gerald Voss, *Tuberculosis Vaccine Initiative, the Netherlands; Global HIV Vaccine Enterprise, USA*
15:00-15:15	Professor Pauline Byakika-Kibwika, *Infectious Disease Institute, Makerere University, Uganda*
15:15-15:45	Discussion Professor Christine Stabell Benn, *Staten Serums Institut, Denmark; Bandim Health Project, Guinea-Bissau* Professor Gary Maartens, *University of Cape Town, South Africa*
15:45-16:00	Coffee/Tea
16:00-17:00	Final summing up and recommendations
17:00-17:15	Closing remarks

Annex 2: List of participants

Name	Institution	Country
Eleni Aklillu	*Karolinska Institute*	*Sweden*
Dissou Affolabi	*Centre National Hospitalier de Pneumo-Physiologie*	*Benin*
Olawale Ajose	*Unitaid*	*Switzerland*
Jorge Alvar	*DNDi*	*Switzerland*
Maryline Bonnet	*Institute of Research for Development*	*France*
Pauline Byakika-Kibwika	*Infectious Disease Institute, Makerere University*	*Uganda*
Christian Burri	*Swiss TPH*	*Switzerland*
Nuria Casamitjiana	*ISGlobal*	*Spain*
Simon Chell	*GSK*	*United Kingdom*
Vanessa Christinet	*CIRES*	*Cameroon*
Bouke de Jong	*Institute of Tropical Medicine*	*Belgium*
Oscar Della Pasqua	*University College London*	*United Kingdom*
Sabine Dittrich	*FIND*	*Switzerland*
Stephan Duparc	*Medicines for Malaria Venture (MMV)*	*Switzerland*
Rashida Ferrand	*London School of Hygiene & Tropical Medicine (LSHTM); Biomedical Research & Training Institute*	*United Kingdom, Zimbabwe*
John Gyapong	*University of Health and Allied Science*	*Ghana*
Catherine Hankins	*AIGHD*	*Netherlands*
Michael Hoelscher	*Ludwig Maximilian University of Munich (LMU)*	*Germany*
Philippe Jacon	*Cepheid*	*France*
Andre Pascal Kengne	*MRC-South Africa*	*South Africa*
Saye Khoo	*University of Liverpool*	*United Kingdom*
Ronan L'Heveder	*Santé Diabète*	*France*
Gary Maartens	*University of Cape Town (UCT)*	*South Africa*
Shabir Mahdi	*National Institute for Communicable Diseases (NICD); University of Witwatersrand*	*South Africa*
Dermot Maher	*WHO-TDR*	*Switzerland*
Maria Fraga Oliveira Martins	*Institute for Hygiene and Tropical Medicine, New University of Lisbon*	*Portugal*
Alessandra Martini	*European Commission*	
Clara Menéndez Santos	*ISGlobal*	*Spain*
Martin Meremikwu	*University of Calabar*	*Nigeria*
Corrine Merle	*WHO-TDR*	*Switzerland*
Francisca Mutapi	*University of Edinburgh*	*United Kingdom*
Victor Mwapasa	*University of Malawi*	*Malawi*
Sebastien Quesney	*Fondation Mérieux*	*France*
Michael Ramharter	*Bernhard Nocht Hospital for Tropical Diseases, Bernhard Nocht Institute for Tropical Medicine and University Medical Center Hamburg-Eppendorf*	*Germany*
Klaus Reither	*Swiss TPH*	*Switzerland*

Name	Institution	Country
Representative	*European Vaccine Initiative*	*Germany*
Morven Roberts	*MRC-UK*	*United Kingdom*
Philippe Sansonetti	*Pasteur Institute*	*France*
Peter G Smith	*London School of Hygiene & Tropical Medicine*	*United Kingdom*
Christine Stabell Benn	*Statens Serum Institut; Bandim Health Project*	*Denmark, Guinea-Bissau*
Marcel Tanner	*Swiss TPH*	*Switzerland*
Marleen Temmerman	*Aga Khan University (AKU) Hospital Nairobi; Ghent University*	*Kenya, Belgium*
Halidou Tinto	*Institute for Research in Health Sciences*	*Burkina Faso*
Reinout van Crevel	*Radboud University Medical Center*	*Netherlands*
Philippe Van de Perre	*Université Montpellier*	*France*
Susan van den Hof	*KNCV*	*Netherlands*
JP Van Geertruyden	*University of Antwerp*	*Belgium*
Remko van Leeuwen	*AIGHD*	*Netherlands*
Gerald Voss	*TBVI; Global HIV Vaccine Enterprise*	*Netherlands, USA*
Alan Winston	*Imperial College*	*United Kingdom*
Dawit Wolday	*Path Medical Services; Mekelle University College of Health Sciences*	*Ethiopia*
Maria Yazdanbakhsh	*Leiden University Medical Center*	*Netherlands*
Alimuddin Zumla	*University College London*	*United Kingdom*
Pauline Beattie	*EDCTP*	*Netherlands*
Montserrat Blázquez-Domingo	*EDCTP*	*Netherlands*
Moses Bockarie	*EDCTP*	*South Africa*
Gabrielle Breugelmans	*EDCTP*	*Netherlands*
Christy Comeaux	*EDCTP*	*Netherlands*
Jean Marie Habarugira	*EDCTP*	*Netherlands*
Dominika Jajkowicz	*EDCTP*	*Netherlands*
Michael Makanga	*EDCTP*	*Netherlands*
Thomas Nyirenda	*EDCTP*	*South Africa*
Ole Olesen	*EDCTP*	*Netherlands*
Lara Pandya	*EDCTP*	*Netherlands*
Monique Surette	*EDCTP*	*Netherlands*

Colophon

European & Developing Countries Clinical Trials Partnership
The Hague, the Netherlands, February 2018

EDCTP2 programme is supported under Horizon 2020, the European Union's Framework Programme for Research and Innovation.

Europe Office
Postal address
P.O. Box 93015
2509 AA The Hague
Netherlands

Visiting address
Anna van Saksenlaan 51
2593 HW The Hague
Netherlands

Phone: +31 70 344 0880/0897
Fax: +31 70 344 0899

Africa Office
Postal address
P.O. Box 19070
Tygerberg 7505, Cape Town
South Africa

Visiting address
Francie van Zijl Drive,
Parowvallei 7505, Cape Town
South Africa

Phone: +27 21 938 0690
Fax: +27 21 938 0569

www.edctp.org
info@edctp.org

@EDCTP

edctpmedia

Writer: Ms. Karin Fischer-Buder (United Kingdom)
Editing: EDCTP staff
Cover photo: Africa interactive - Medical staff at the Amana Hospital in Dar es Salaam, Tanzania *(TRIP project led by Dr Sayoki Godfrey Mfinanga, National Institute for Medical Research, Tanzania)*.
Design: Studio Duel, The Hague, the Netherlands

The power of sharing science

The EDCTP2 programme is supported under Horizon 2020, the European Union's Framework Programme for Research and Innovation.

www.edctp.org
info@edctp.org
@EDCTP
edctpmedia