



EDCTP

European & Developing Countries Clinical Trials Partnership

STAKEHOLDER MEETING

REPORT ON
HIV/AIDS

LISBON, PORTUGAL

3-4 SEPTEMBER 2013



Towards the second EDCTP programme

The EDCTP Stakeholder Meeting on HIV/AIDS is part of a series of thematic stakeholder meetings planned to contribute to the shaping of strategy and funding approach of the second EDCTP programme. EDCTP held meetings on Neglected Infectious Diseases, Malaria, Tuberculosis and other mycobacterial infections, as well as on Research Ethics Review and Regulatory Affairs. The Stakeholder Meeting on Capacity Building will take place in Berlin on 3 July 2014.

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EDCTP was created in 2003 as a European response to the global health crisis caused by the three main poverty-related diseases (PRDs) of HIV/AIDS, tuberculosis and malaria. Currently

EDCTP is a partnership between 16 European countries, the European Union and sub-Saharan African countries. The aim of the programme is to accelerate the development of new and improved drugs, vaccines, microbicides and diagnostics against HIV/AIDS, tuberculosis and malaria through a balanced partnership of European national research programmes on PRDs with their African counterparts in collaboration with the pharmaceutical industry and like-minded organisations.

The second EDCTP programme will start in 2014 as part of the European research framework programme Horizon 2020. Its scope is based on the current objectives and achievements and will be expanded to include: all clinical trial phases I-IV including health services optimisation research; other neglected infectious diseases; closer collaboration with industry, like-minded product development partners and development agencies; and collaborative research with other developing countries outside sub-Saharan Africa when possible and desirable.

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Acronyms and abbreviations

AIDS	Acquired immunodeficiency syndrome
ANRS	Agence Nationale pour Recherche sur le SIDA et Hépatites Virales (French agency for AIDS and viral hepatitis research)
ART	Antiretroviral therapy
CHAPAS	Children with HIV in Africa-Pharmacokinetics and Adherence of Simple Antiretroviral Regimens
EDCTP	European & Developing Countries Clinical Trials Partnership
EDCTP ₂	Second EDCTP programme
EFTA	European Free Trade Association
Horizon 2020	European Union framework programme for research and innovation that will run from 2014 to 2020
Gates Foundation	Bill & Melinda Gates Foundation
HIV	Human immunodeficiency virus
HPV	Human papilloma virus
MSM	Men having sex with men
PMTCT	Prevention of mother-to-child transmission
PrEP	Pre-exposure prophylaxis
TB	Tuberculosis
UNAIDS	Joint United Nations Programme on HIV and AIDS
UNICEF	United Nations International Children's Emergency Fund
WHO	World Health Organization

1. Executive summary

This meeting was part of the preparations for the second programme of the European & Developing Countries Clinical Trials Partnership (EDCTP2). The two-day event was attended by 74 participants, including researchers, representatives of product development partnerships and the pharmaceutical industry, policy makers, funding agencies and other like-minded organisations.

Discussions were structured around the following presentations, after each of which participants asked questions and made comments:

- Plans and progress towards EDCTP2 – Prof. Charles Mgone
- Keynote address – Prof. Gita Ramjee
- Treatment and Care I: product portfolio – Dr Paula Munderi
- Treatment and Care II: paediatrics, PMTCT – Prof. Philippe Van de Perre
- Treatment and Care III: implementation research – Prof. Linda-Gail Bekker
- Vaccines (prophylactic and therapeutic): product portfolio – Dr Pontiano Kaleebu
- Prevention product portfolio: microbicides, PrEP – Prof. Sheena McCormack
- Partnerships and collaborations – Panel discussion.

Generally, it was suggested that it is important to take advantage of clinical trials to improve our basic science knowledge about HIV infection and AIDS. Capacity building is important, but it will be essential to go beyond training and infrastructure development; we need to ensure sustainability. Community involvement is essential but this should not be limited to a presence, communities should be empowered; it was suggested that training could help to improve their involvement. Task shifting to the local level needs to be increased for treatment delivery but also training. Multi-disciplinary research is needed to address many aspects of treatment adherence, risk perception and development of novel methods for evaluation,

as well as ethical, human rights and regulatory issues.

The efforts to identify a cure for HIV/AIDS and to eradicate the HIV reservoir were discussed and what role, if any, EDCTP should have in these efforts was debated.

The comments shared during the meeting are summarised below in six main themes: treatment; prevention strategies; vaccines; adherence strategies; capacity building and partnerships. It was clear from the discussions over the two days that there is still a lot to be done in all areas. It will be important for EDCTP to define clearly its focus so that the actions it undertakes and the projects it funds will make a difference.

Treatment

- Research to assess new treatments and healthcare systems (efficient delivery, improved adherence to treatment, and minimised number of patients not reached by the system)
- Research targeted at specific populations such as women (particularly pregnant women), children, adolescents and the elderly
- There are many new molecules in various phases of clinical development but we need guidelines for prioritising which ones should be taken forward
- Evaluate dose optimisation, new formulations, reformulations and delivery systems
- Identify better second- and third-line treatments
- Improve clinical trial capacity in Africa; not just training but also building and sustaining facilities (laboratories)
- HIV-positivity is now a chronic disease; health systems need to adapt to this. They need to know how to treat co-morbidities and how to deal with ageing

- Better systems for post-marketing surveillance are needed in order to identify resistance, long-term adverse effects and drug-interactions. Is there a role for EDCTP?
- Determine when treatment should be started; there is a trend to earlier treatment but when individuals are asymptomatic, they do not necessarily perceive their risk correctly. Multidisciplinary research is needed to understand the motivation for adherence and risk perception
- Explore innovative treatment delivery systems and promote task shifting to communities in order to:
 - Reduce waiting times
 - Facilitate treatment delivery
 - Keep patients in care
 - Improve adherence.
- Improve the transition of adolescents to adult healthcare
- Treatment guidelines are evolving rapidly but they are not always evidence-based. Approaches other than classical randomised controlled trials are needed to provide more robust evidence for the guidelines.
 - Explore combined contraceptive and HIV prevention devices (e.g. rings)
 - Improve prevention in girls and women: twice as many girls than boys under 15 years of age are HIV-positive and 58% of the overall HIV-positive population is female
 - Strategies for populations at risk, e.g. men having sex with men (MSM), and sex-workers
 - Reach the targets for prevention of mother-to-child transmission. Improve access to ART for HIV-positive pregnant women in low-to-middle income countries and improve treatment adherence
 - More effective treatments to prevent transmission via breast milk; the virus seems to be less susceptible in this environment.
- Exposed but uninfected infants should be studied in order to understand their protection mechanism. Establish a cohort to be studied and followed, as these individuals tend to become lost to the system.

Prevention strategies

- Optimise prevention strategies until effective vaccines are available
- Combination strategies will probably be most effective, but require tailoring to the needs of specific populations
- Innovative trial designs for assessment of combination prevention strategies
- Innovative delivery systems with longer-acting formulations to avoid the need for ‘a-pill-a-day’, or formulations that can be used as needed
- Good adherence is needed to ensure effectiveness; improve understanding of the motivators for adherence
- Understand what different populations need in terms of prevention. Are the available prevention measures accepted?

Vaccines

- Many candidate vaccines were tested, but only one has shown moderate efficacy (30% reduction in HIV infections)
- Vaccines for specific populations, such as breast-fed infants, children and pregnant women
- Include breastfeeding mothers in clinical trials: maternal immunisation could provide protection to infants
- Improve our understanding of the immune response (B cell, T cell, combined)
- Local laboratory capacity building is essential to make vaccine trials in Africa possible.
- Virus inhibition assays need to be optimised and standardised to enable the comparison of candidate vaccines
- Practice vaccine trials could be conducted in Africa to prepare capacity for HIV vaccine trials

- Even if no vaccine is available yet, it is necessary to start thinking about how to make a vaccine available in Africa (taking into account expertise from HPV and other adult vaccination programmes)
- Therapeutic HIV vaccines have not shown much efficacy so far; other candidates must be identified.

Adherence strategies

- Adherence to therapeutic and preventive treatments is essential for effectiveness
- Poor adherence can result in the development of resistance. Reasons for non-adherence to treatment are often multifactorial; multi-disciplinary research is needed to understand these reasons and possibly identify ways of improving adherence
- Formulations that have improved bioavailability, reduced drug concentration, lower costs, fewer adverse effects, prolonged-release, less frequent administration, are needed to improve adherence
- Healthcare systems research could contribute to improved adherence by facilitating access to treatment (community involvement, task shifting, and empowerment).

Capacity building

- Capacity building should not be limited to training and infrastructure development but ensure sustainability
- Clinical trial capacity needs to be improved to increase the number of trials conducted in Africa
 - We need to understand why the pharmaceutical industry seems reluctant to conduct clinical trials in Africa
 - Networks of excellence should be available to ensure the required levels of subject recruitment.
- Laboratory capacity needs to be improved through local pharmacokinetics and pharmacodynamics facilities, improved

laboratory standards, and standardised testing (such as for vaccines)

- Treatment delivery capacity can be developed by task shifting to local communities.

Partnerships

- There are many actors in the HIV/AIDS research area with different, but often complementary remits
- Important to share information and avoid duplication
- Important to examine what partnerships can be developed, e.g.:
 - WHO/UNAIDS for ethical, human rights and clinical trial methodology issues
 - Gates Foundation for large-scale vaccine trials, including in countries outside Africa.
- The new governance structure for EDCTP₂ should facilitate the development of partnerships with simpler administrative rules
- EDCTP needs to clarify its priorities as it cannot do everything; for some areas partnerships could be useful
- EDCTP could play the role of broker for organising co-funding of larger clinical trials.

The wide range of comments and suggestions made by participants over the two days showed how much remains to be done in the HIV/AIDS field. The general recommendations and priorities identified by the participants will inform EDCTP in the planning of its programme for EDCTP₂.

2. First day

The HIV stakeholder meeting is part of a series of thematic stakeholder meetings held in preparation for the second programme of the European & Developing Countries Clinical Trials Partnership (EDCTP2). The two-day event took place in Lisbon, Portugal and was hosted by ISCTE-University Institute of Lisbon and the Portuguese Foundation for Science and Technology (FTC). It was attended by 74 participants, including researchers from academia, representatives of product development partnerships and the pharmaceutical industry, policy makers, funding agencies and other like-minded organisations.

The aim of the meeting was to identify key challenges and opportunities for EDCTP in advancing research in HIV/AIDS and the financial strategies that are required.

Plans and progress towards EDCTP2: Prof. Charles Mgone

Professor Charles Mgone, EDCTP Executive Director, recalled the mission, objectives and scope of EDCTP. He gave a summary of the grants awarded and the trials supported so far. He also highlighted the concept of partnership which is seen as the basis of EDCTP's programme and stressed the importance of the regional Networks of Excellence in EDCTP's achievements.

The second phase of the programme will commence in 2014. Some of the novel features of EDCTP2 include larger and more costly phase III clinical trials, extension of activities to cover neglected infectious diseases and also phase IV trials, activities initiated by participating states, and an increased number of integrated activities and projects conducted jointly with partners.

Criteria for establishing priorities for action will include disease prevalence, product opportunities, balancing immediate and long-term priorities, and maintaining a balance among clinical trial phases. EDCTP has undertaken research landscape mapping, and developed strategic and operational business plans.

Membership is planned to be broadened, particularly with the newer Member States that joined the EU since 2004. EDCTP2 will build on the current programme to continue its work. There will be a change in the EDCTP's legal status, from a European Economic Interest Grouping (EEIG) to an Association under Dutch law, so that non-EU and non-EFTA membership will be possible.

The integrated activities and projects will continue to be run and funded by EDCTP but with a simplified approach to co-funding (centralised administration by EDCTP), and according to the same rules of participation as under Horizon 2020. Sharing of common facilities will be promoted through funding of participating states initiated activities (PSIA). There will be joint activities, including co-funding with other partners (public/private), and earlier involvement of partners in the project development process.

The first HIV meeting, held in Madrid in 2007, concluded that paediatric and second-line treatment were priority areas for research. Since then meetings were held in Oslo (microbicides, 2007), Antwerp (vaccines, 2007), and Lisbon (HIV-TB coinfection, 2009). The priorities that were identified included, 1) studies to establish when to start ART; 2) pharmacokinetic and pharmacodynamic studies; 3) vaccine (phase I and II) trials; 4) capacity building (including preparing sites for participation in clinical trials); and 5) exploring attitudes of adolescents about participating in clinical trials.

Prof. Charles Mgone recalled the expected outcomes from the meeting:

- Review of the current state of the research
- Identification of key research areas with opportunities and threats
- Recommendations for the second EDCTP HIV/AIDS programme.

Keynote address: Prof. Gita Ramjee

Professor Gita Ramjee, Medical Research Council of South Africa, held the keynote address on the state of HIV research and treatment. She commenced by saying that much progress had been made in HIV testing and that more rapid HIV confirmatory tests were available. Treatment for HIV/AIDS had greatly improved, with the availability of triple and combination therapies and the identification of different targets for therapy.

Despite this progress, there are a number of outstanding problems. For example, when should treatment be started, delayed or as soon as possible? Starting treatment early is now favoured, but there is a risk of uncontrolled viremia at all CD4 levels. Also drug resistance can arise from poor treatment adherence or viral mutation. Poor treatment adherence is due to a combination of factors that can involve the individual, the health system, the complexity of treatment and/or the associated adverse events.

Prevention of HIV infection is possible at both the individual and community levels. Biomedical prevention strategies have been developed. Strategies for prevention of mother-to-child transmission have resulted in a steady decline in the incidence of HIV-infected new-borns, but better preventive strategies are needed. Good adherence to anti-retroviral therapies is required; knowledge of risk perception

is important so that an individual can be motivated to adhere to treatment.

Twice as many girls aged 15-24 years are HIV-positive than boys; generally women account for 58% of all HIV-positive populations. The prevalence of HIV-infections has declined in the last decade but this hides an increased incidence, suggesting that the prevention strategies are not working. Among the risk factors for women to seroconvert are age (<25years) and having another sexually transmitted infection. Contraception-use could affect the risk of HIV infection since they can induce changes in immune functions and the genital tract. One type of progestin-only injectable contraceptive has been reported to be associated with an increased risk of seroconversion. However, several observational studies have provided inconclusive results; therefore better evidence from randomised clinical trials is needed.

Recent results from research demonstrate that two microbicides (nonoxynol-9 and cellulose sulphate) may increase women's risk of infection. Other microbicides have been shown to be safe, not to lead to a higher risk of infection, but they are not effective. Results from some current trials suggest that tenofovir gel, used vaginally before and after coitus, may reduce the incidence of HIV infection in women. Between 1992 and 2012, 10 microbicides have been investigated, but only one has demonstrated proof of concept; but, as with all these strategies, good adherence is essential for effectiveness.

Vaccines can offer prevention, but none has been identified so far. Integrated, tailored combination prevention strategies are needed; there is no single magic bullet.

There is an urgent need to integrate prevention and treatment of HIV and tuberculosis in high endemic areas. Modelling studies have shown that a comprehensive approach is best,

especially in endemic areas. EDCTP could develop platforms for integrated research.

Comments

In the discussion that followed Prof. Ramjee's presentation, the following comments were made:

- Community involvement is essential in biomedical research and service delivery to improve implementation
- EDCTP should prioritise the evaluation of combination prevention approaches; an alternative to the randomised, control trial design is needed
- 'One size doesn't fit all': tailored strategies should be implemented, but assessment requires large sample size, with implications for cost
- Contrary to common belief, poorer communities have lower levels of HIV-infection; urban communities have higher levels than rural communities
- Successful ART has turned HIV into a chronic disease but sub-Saharan African countries are not prepared for chronic disease health care; health system organisation should be assessed and prepared to address issues such as: chronic diseases, ageing, long-term toxicities, migration, standardised access to care
- More evidence about progestin contraceptives is needed
- The impact of ART in reducing incidence (not just in couples) needs to be measured in real-life settings
- Higher priority should be given to certain key populations in sub-Saharan African, i.e. MSM, intravenous drug users, and sex workers.

Treatment and Care I: Dr Paula Munderi - Product portfolio

Dr Paula Munderi, Medical Research Council and Uganda Virus Institute, Research Unit on AIDS, Uganda, presented an introduction to the global product portfolio based on the pipeline report of the Treatment Action Group which is regularly updated¹.

She recommended focusing research on specific issues regarding treatment (such as tolerability, resistance, convenience, special populations and cost) in order to overcome the limitations of the current treatment regimens. At present, tenofovir is the preferred product. On-going studies assess reformulations, co-formulations and reduced doses for similar safety and efficacy but improved bioavailability and potentially fewer side-effects.

Certain populations, such as children, women of childbearing age and patients with HIV/TB co-infections are not included in the drug development studies, which are generally done in the North. What is the role of EDCTP in post-registration surveillance studies when approved treatments are used in these special populations?

Currently, there are not enough investigator-initiated studies in Africa and there is a need to increase their number, requiring the development of more clinical trial sites in Africa, with sufficient resources and infrastructure as well as appropriate regulatory and ethical oversight.

Diagnostic tests are essential for assessing toxicity, co-infections and efficacy of therapy (CD4 levels and viral load). Finally, there is a need to remain open to the (still early stage) approach towards 'a cure for HIV' and the 'eradication of the HIV reservoir'.

¹ The Treatment Action Group 2013 Pipeline report: www.treatmentactiongroup.org/pipeline-report/2013

Dr Munderi concluded by offering topics for discussion of the role of EDCTP:

- How can EDCTP enhance the treatment pipeline?
- What is its role in assessment of diagnostic tests?
- What is its role in research for special populations?
- What is its place in post-marketing studies?
- What is EDCTP's role in the search for an HIV cure?
- What is the best model for capacity building?

Comments

- Monitor drug-drug interactions in post-marketing surveillance studies in different populations; not just genetic as other factors e.g. malnutrition, also have an impact
- Place for pharmacogenomics research in EDCTP's agenda?
- Pro-drugs (in early-stage development) could enable higher intracellular concentrations with lower dose and fewer side effects. Identification of fast and slow activators, which may have a role in toxicity
- It is essential to increase the clinical trial capacity in Africa, particularly to improve understanding of pharmacodynamics and pharmacokinetics in infants
- Community involvement is essential; presently, many community representatives lack sufficient education/training. Could EDCTP extend its role to supporting the training of people in their role as community representatives?
- Could EDCTP create a platform or interface on ethics to address the issues regarding conducting clinical trials in Africa?
- Is there a role for EDCTP in the HIV Cure Initiative, particularly regarding infants in low-income countries? For example, the identification of African 'Mississippi babies' (the 'Mississippi baby' was started on ART

at approximately 30 hours instead of the usual 6-weeks); earlier diagnosis is needed to improve health services

- Strategies to reduce HIV reservoirs should be considered while there is no cure yet
- EDCTP should be involved in defining more adequate second-line and third-line treatment
- EDCTP could support better research for diagnostic tools: current studies use laboratory criteria, not patient-reported outcomes
- In West Africa, emergence of HIV2 should be included in the research agenda
- Is there a role for EDCTP with regard to adherence and resistance studies (crucial issues for effective treatment)?

Treatment and Care II: Prof. Philippe Van de Perre - Paediatrics and prevention of mother-to-child transmission

Professor Philippe Van de Perre, University of Montpellier (France), gave an overview of the research in paediatrics and studies of the prevention of mother-to-child transmission of HIV. He also shared research topics that could be prioritised in this area.

Global targets for the prevention of perinatal HIV transmission set (in 2009) for 2015 include: elimination of perinatal infections (i.e. reduction to <5%); a 90% reduction of new infections from 430,000 in 2009 to 43,000 in 2015 as well as a 50% reduction of HIV-associated maternal mortality. In 2011, there were 330,000 new infections, only a 23% reduction due to the fact that too few pregnant HIV-positive women receive ART in low-to-middle-income countries.

The global guidelines for PMTCT were revised in June 2013 in the WHO report published in partnership with UNICEF and UNAIDS.

According to Prof. Van de Perre, the current recommendations are not evidence-based. For example, the ‘evidence’ for option B² comes from modelling studies, best guess and feasibility. There is some evidence that treatment can reduce most means of transmission, but not transmission during breastfeeding; the virus in breast milk does not seem to be affected by the treatment. There is sub-optimal adherence in this population (~53% still taking treatment at 12 months in a study of 20,000 women; this is not good for option B+). In addition, there is a high-rate of multiclass resistance in children who become infected via a mother on ART.

Guideline option A is being assessed in an on-going clinical trial. The results for the 1,200 children treated for 12 months are expected soon. The preliminary analysis of data for 750 children showed an efficacy of 1.0% at 12 months, which perhaps suggests option A should be removed from the guidelines.

The prevalence of HIV infections is increasing, particularly in girls older than 15 years of age. Results from the CHER trial (immediate ART versus deferred ART) showed a 76% reduction in mortality, most deaths occurring within six months (before 10 months)³.

This raises the issue of the technical and organisational challenges of ensuring early diagnosis. For example, there is a trend for early initiation of ART, but only for approximately 20% of children younger than 1 year, which is not sufficient. There is also a lack of knowledge on

paediatric formulations of ART, some of which are being evaluated in the CHAPAS⁴ studies.

The following issues were raised as unanswered research questions in this area:

- What is the community effect of options B/B+?
- Would it be possible to optimise treatment by combining options B/B+ and A? What is the epidemiology and best treatment for infant and maternal co-infections?
- Would extra-long-acting drugs improve treatment adherence?
- How can treatment be simplified?
- What is the best way to operationalise access to prevention and therapy?
- How can children’s access to treatment be improved?
- How can we achieve earlier paediatric diagnosis?
- What is the best way to ensure continuum of care and prevention when children become adults?
- What is the most effective point of entry for an integrated care and prevention programme?

Comments from participants

- The guideline options B/B+ are not optimal in places with low fertility (e.g. South Africa)
- We do not know the impact of treatment on children’s development (immune system and general), including long-term ART effects and effects of second line treatment
- We need to improve our understanding of postnatal mother-to-child transmission of HIV taking into account the physiological differences in the neonate compared to the mother

2 Option A: Infant pre-exposure prophylaxis; Option B: Maternal prophylaxis during breastfeeding; Option B+: Lifetime ART for all HIV-infected mothers, regardless of clinical or immunological status.

3 Early time-limited antiretroviral therapy versus deferred therapy in South African infants infected with HIV: results from the children with HIV early antiretroviral (CHER) randomised trial. Prof Mark F Cotton et al.: *The Lancet* - 9 November 2013 (Vol. 382, Issue 9904, Pages 1555-1563).

4 Children with HIV in Africa Pharmacokinetics and Acceptability/Adherence of Simple Antiretroviral Regimens (CHAPAS-3) www.edctp.org/Project_Profiles.245.o.html?&no_cache=1

- It is important to follow up and evaluate the exposed uninfected children in order to understand their outcome
- Linkage to care records could reduce the loss to follow-up of children between birth and treatment
- We need to understand the cultural component of breastfeeding; it is not always acceptable to breastfeed for 12 months
- The current recommendations for the treatment of pregnant women are not based on clinical trial evidence but on meta-analyses of observational studies. So far, there are no major safety concerns, but the effectiveness of treatment needs to be evaluated. This could be assessed in post-marketing active surveillance studies
- There is a need to improve the pharmacokinetic modelling capacity in African institutions.

Summary

- EDCTP's prime focus is the evaluation of new and improved interventions
- A major challenge (due to the organisation of health systems) is to find the children/teenagers who need to be treated
- Better paediatric formulations are needed
- A cohort of exposed but uninfected children should be established in order to improve knowledge about HIV-susceptibility.

Treatment and Care III: Prof. Linda-Gail Bekker - Implementation research

Professor Linda-Gail Bekker gave a brief introduction to the global expansion of ART treatment since 2003. The most recent WHO guidelines (2013) have set the threshold for treatment at <500 cells/mm³ in developing countries. In South Africa with already almost 2 million people on ART, this means a scale-up

of the treatment programme with an additional 1 million treatment initiations.

In her presentation, Prof. Bekker discussed the challenges resulting from this scale-up for all aspects of individual treatment along the spectrum of testing, up-take, adherence and retention. The different aspects (drugs, monitoring, co-morbidities, and health systems) were presented as areas of research.

Currently, two clinical trials, START⁵ and TEMPRANO⁶, are assessing early treatment.

The treatment cascade:

- People are lost to care at all levels
- About 25% of people unaware of their HIV-status account for approximately 54% of new infections
- Once people's status becomes known and they are included in treatment programmes, the challenge is to keep them in care and on treatment
- It is important to recognise the three steps to adherence: initiation, persistence, performance
- It is recommended to collaborate with social scientists to understand the motivation of HIV-positive people to stay on treatment
- Strategies to improve adherence need to be assessed. The important elements are: modern means of communications; decentralisation of services towards the local level; equally, task shifting so that people assume responsibility locally.

The key populations that need consideration for future research are:

5 Strategic Timing of Anti-Retroviral Treatment (START) study; <http://insight.cbr.umn.edu/start>

6 The Antiretroviral Therapy Cohort Collaboration Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies. *The Lancet*, Volume 372:293-299. (26 July 2008). www.thelancet.com/journals/lancet/article/PIIS014067360861137/abstract

- Young children (under 3 years of age) who have TB and HIV co-infection (few therapeutic options). Additionally, ART treatment is often suboptimal in children and this can lead to significant resistance
- Adolescents who were infected perinatally are becoming an important population. For example, in South Africa there are about 400,000. It is estimated that a plateau will be reached in 2016 when this group will represent about 6% of the total HIV-positive population. A problem is the transition to adult care; there are no studies to identify the best strategies.

Issues that need to be addressed at individual, system and community levels:

- The population of 'unawares' is an important source of HIV transmission. Strategies should be developed to reach them for HIV testing, treatment (HIV-positive) or prevention counselling (HIV-negative)
- Improve understanding of HIV-positive asymptomatic population
- Improve treatment acceptance and adherence
- Reduction of viral reservoirs and finding a cure.

Comments

The following issues were then raised by several participants:

- Only 26% of those who need treatment are receiving it. EDCTP could take a leadership role in exploring trial designs for assessing treatment implementation (health services research) to improve the quality of evidence for public health interventions; these studies are specific to the healthcare setting
- There are different models involving various ways of task shifting to communities, e.g. an adherence clinic in South Africa distributes treatment to 100 people in one

hour; and in Bangladesh there is a treatment delivery service which works with 'expert patients'

- Look at innovative systems for delivery; develop partnerships for testing different delivery modes which can use randomisation
- Support studies in healthcare research with rigorous study designs
- Integrated actions and partnerships with other agencies; collaboration with economists and social scientists
- HIV infection is now a chronic illness, which has implications for long-term complications of chronic treatment, but also for other diseases. To improve adherence also understand the motivation of healthcare workers as well as patients.

Summary points from the Chairs

Challenges for the future research agenda

- Embrace new evaluation methodologies, e.g. combination strategies for prevention
- Identify needs in special populations:
 - Infants often are lost to care in their first year of life
 - Children: effects of long-term treatment; treatment failure; factors explaining status 'exposed but uninfected'
 - Adolescence: treatment optimisation; transition to adult care
 - Women of child-bearing age: interaction with contraception; reproductive health issues.
- Increase clinical trial capacity in Africa to assess:
 - Dose optimisation
 - New formulations (less serious side effects will improve adherence); longer-acting drugs; lower costs
 - Increase local capacity for pharmacokinetics, pharmacodynamics, and pharmacogenetics studies
 - Second- and third-line treatments

-
- Diagnostics, combination prevention and treatment strategies.
 - Should EDCTP be involved in the search for a cure?
 - Improve understanding of drivers for adherence or motivation (healthcare workers and patients) and of risk perception.

Challenges for healthcare systems

- HIV infection is now a chronic disease, but healthcare systems have not yet reacted to this (co-morbidities, ageing)
- Results from studies in the North cannot be extrapolated to sub-Saharan Africa because of weaker healthcare systems
- Increase capacity to meet increasing demand
 - Keeping patients in care
 - Reducing waiting times
 - Task shifting to local levels
 - Innovative treatment delivery systems
 - Improved community partnerships/participation (Good Participatory Practices).
- Strengthening of ethical and regulatory situation
- Rapidly changing guidelines
 - Do we need to critically appraise them?
 - When should treatment start?
- Surveillance for resistance and toxicity of drug-interactions.

3. Second day

Preventive and therapeutic vaccines: Prof. Pontiano Kaleebu - Product portfolio

Professor Pontiano Kaleebu discussed the global portfolio of candidate preventive and therapeutic HIV vaccines. Only one (RV144 trial) of the six HIV-1 vaccine efficacy trials has reported a modest effect (31.2%). It was found that high levels of IgG to variable regions 1 and 2 of the HIV-1 envelope proteins may contribute to protection whereas high levels of IgA to the envelope may diminish the effects of protective antibodies⁷. This trial also illustrates how data from clinical trials can provide feedback for basic research.

Human neutralising monoclonal antibodies have been isolated but have not been tested yet. There are a number of combination vaccine candidates which have shown good protection in macaques. In the pipeline (in clinic currently to next three years) there are 36 phase I/II and one IIB efficacy trials and 20 prime/booster trials, but just six trials are conducted in sub-Saharan Africa which is fewer than before.

Several organisations are involved in trials to test different candidate vaccines, including T cell vaccines, B cell vaccines and CD8 vaccines: the International AIDS Vaccine Initiative (IAVI); National Institute of Allergy and Infectious Diseases (NIAID); UK HIV Vaccine Consortium (UK HVC); and the French 'Agence Nationale pour Recherche sur le SIDA et Hépatites Virales' (ANRS).

Vaccines based on human broadly-neutralising monoclonal antibodies are being tested as therapeutic vaccines as well as prophylactic vaccine (e.g. for babies on breast feeding); results with therapeutic vaccines have been disappointing.

Topics that were suggested for discussion:

- The role of EDCTP in vaccine design
- Epidemiology: methods to identify and follow specific populations; cost-effective methods for estimating incidence; and social/behavioural studies to improve understanding of the factors that influence retention
- Clinical trials: identification of products that should be taken forward
- Use of data from clinical trials to answer also basic science questions, not just to evaluate safety and efficacy; we need to investigate co-infections and immune activation
- Conducting small trials in high-risk populations
- Standardisation of laboratory procedures is essential
- Passive immunotherapy and prophylactic vaccines in children should be assessed, although there are not many candidates for phase IIB/III trials. Practice trials could be used to prepare centres for when candidate vaccines will be available
- Role of EDCTP in issues such as regulatory support and vaccine production, as well as in capacity building, especially in supporting training for young people
- EDCTP's role in networking and advocacy with initiatives such as the new African AIDS Vaccine Programme (AAVP)?

Comments

In the discussion that followed Prof. Kaleebu's presentation, the following points were raised:

- EDCTP could set-up a vaccine task force to explore:
 - International collaboration with existing initiatives, e.g. the European Vaccine Effort against HIV/AIDS (EuroVac), to identify candidate vaccines
 - Consolidation of cohorts funded under EDCTP1 (non-progressive infections) either alone or in partnership

⁷ Haynes et al., *NEJM* 2012;366:1275-86

- Laboratory standards: EDCTP could partner with other partners working in this area such as the African Society for Laboratory Medicine (ASLM). It is important to note that building of laboratory infrastructure is relatively simple, but sustaining the laboratories' quality for the long-term is a challenge.
- Immune responses to HIV are not well understood and candidate vaccines produce surprises; much is still unknown about the immune response to vaccines targeting either infection or disease:
 - The immune system works as a whole, not just with B-cells or T-cells
 - Understand how to inhibit the destruction of T-cells to prevent disease; both neutralising and non-neutralising antibodies should be studied, as well as infection and inflammation
 - Mucosal immunology: as this requires fresh samples, smaller studies could be conducted with analysis performed locally.
- Vaccine research should be a reiterative process so that we can maximise what we learn from trials; it requires local capacity as well as international cooperation
- Vaccines for specific populations: infants, young children, pregnant women
- No correlates of protection: the virus inhibition assay needs to be optimised so it can be used to compare different vaccine candidates
- Developing vaccines is important, but we need to start thinking already about how to make vaccines accessible in Africa
 - Use experience gained from HPV programmes
 - Use experience with adult vaccination; HIV vaccination is more complicated because of the need for booster, etc.

Prevention product portfolio: Prof. Sheena McCormack - Microbicides and PrEP

Professor Sheena McCormack presented a short overview of the prevention portfolio and the status of the field. Fortunately, successful HIV treatment has resulted in an ever-growing population of people living with HIV. Nevertheless, this puts a huge burden on patients and health care systems. Therefore, the next priority is to increase the use of PrEP and microbicides to prevent subjects becoming HIV-positive.

Truvada® has been licensed for PrEP, initially in MSM and discordant couples, but the indication has recently been extended to people who use drugs intravenously. There are also many ongoing PrEP and microbicide studies assessing different delivery modes: gel, ring, oral and topical applications, as well as event-related (rather than a-pill-a-day) delivery. Since HIV infection occurs within five days of 'exposure', we need to re-evaluate the current practice of 28-day post-exposure prophylaxis.

Rings are expensive delivery devices, but as they are being introduced in Africa for contraception, they could be combined with a microbicide product to increase the number of women being protected and thereby decrease costs. In the future, novel delivery devices could include nanotechnology. Some implementation studies have been set-up, for example, rectal tenofovir gel for MSM.

There are several ethical challenges regarding evaluation: one cannot put HIV-negative subjects at risk in trials. Also, the availability of effective PrEP and microbicides could increase the likelihood of people engaging in risky sexual behaviour which could increase demands on health facilities. The MDP 301 study assessed women's use of condoms and

gel and provided results for condom use with and without gel at last sex act; different trial sites showed disparate results.

The key questions regarding adherence are why women did not use the products they were given, and how we are going to test new interventions as effective interventions are rolled out. Clinical trials are highly regulated and adherence to treatment is high. This is unlikely in real-world situations where people are not supervised and adherence is usually low. Men seem to do better than women. In clinical trials adherence ranged from 81% in the Partners trial to <30% in the FEM-PrEP trial. The level of adherence correlated with the efficacy, so although in the FEM-PrEP trial no efficacy was observed, perhaps with better adherence we could expect better efficacy. Generally, if adherence was low or non-existent at the beginning, it stayed low. Correlates of low adherence are the same as the risk factors for HIV. Particularly (young) women and MSM should understand the need for PrEP and accept the available treatments. Personal stories, multidisciplinary approaches and stronger community voices could improve adherence to PrEP. The PROUD Pilot trial randomised MSM having unprotected sex to immediate or delayed (12 months) Truvada to assess if using PrEP would encourage them to stop condom use; other motivators were shown to be more important (friend gets HIV, start of relationship).

Potential priorities for EDCTP in this area:

- Mobilisation of new expertise in clinical projects, e.g. social scientists, anthropologists, health psychologists, social marketers, health economists
- Increased capacity for assessing formulations and improved methods as well as local capacity for vaginal, cervical and rectal biopsies, mucosal sampling and specimen processing

- EDCTP could have a role in developing new partnerships by mobilising other donors to make larger trials (e.g. equivalence trials) possible.

Comments

In the discussion that followed Prof. McCormack's presentation, the following comments were made:

- Clinical trial capacity needs to be reinforced (general consensus)
- PMTCT is a form of PrEP so it should not be treated separately; there is a need to communicate and share knowledge and experience; EDCTP could stimulate collaboration
- Combined targeted PrEP/microbicides will be important until vaccines are available and perhaps could be used in combination. Delivery technology is as important as the drug. Has EDCTP explored all possible technologies to provide choice for patients?
- In clinical trials, adherence is difficult when one arm receives placebo (use of placebo ethically not acceptable); therefore, a comparator should be used that has shown some level of efficacy rather than placebo. As a precedent, FDA does not require placebo-controlled trial for approval of a contraceptive
- New trial designs are needed; EDCTP could bring together relevant stakeholders
- Phase IV trials, follow-up and surveillance are needed to understand uptake in real life settings. Is there a role for EDCTP?
- Effective prevention requires a true perception of risk. Is there a role for EDCTP in supporting studies of risk perception, especially among women?
- Is there a role for EDCTP in engaging regulators and politicians?

Partnerships and collaborations: Panel presentations

Representatives from nine key organisations gave brief presentations about their current activities in HIV/AIDS research.

Dr Alessandra Martini, from the European Commission, Directorate General for Research and Innovation, reported that 27 projects in the field of HIV research had been funded under FP7 to the amount of 130.6 million euros. This extensive programme includes a Network of Excellence supporting cohort studies, a project to develop a point-of-care diagnostic device for the combined detection of HIV and syphilis, and other projects on the development of nine candidate vaccines and other novel molecules in the pipeline.

Dr Ricardo Pereira, Scientific Officer for the Foundation for Science and Technology, Portugal; founding member of EDCTP) reminded the audience that the HIV/AIDS researchers in Portugal were a small scientific community that fortunately has grown over last 20 years. The way forward is to build on the existing community, involving all the disciplines working in this area and encouraging collaboration between partners with complementary capabilities.

Dr Pat Fast, Chief Medical Officer at IAVI, said that the goal is to develop an HIV vaccine that is effective, safe and affordable. Monoclonal antibodies have been produced from African donors, which should ensure the vaccines will work against African viruses. She stressed the importance of viral epidemiology, referring to the example of a study in fishing villages which showed a high incidence in the population, not just among fishermen. This knowledge can be used to design trials that are adapted to the epidemiology. She also mentioned the need for clinical trial technical platforms and capacity.

Mr Tom Lutalo, Rakai Health Sciences Programme - Uganda Virus Research Institute, highlighted how collaboration with EDCTP has resulted in a partnership with the National Institutes of Health (NIH) and the Gates Foundation for capacity building, including the training of junior staff. This has enabled services to be scaled up. The impact evaluation showed that in most communities in Uganda, men come to clinics but women do not. The institute has also set up international collaborations with universities, such as, Johns Hopkins and the London School of Hygiene and Tropical Medicine.

Dr Wendy Snowden, from ViiV Healthcare Ltd, pointed to ViiV Healthcare's collaborative international study programme which has been running for 15 years. It is important that programmes have clear objectives, and that the results are generalisable and publishable. Its partnerships involve big networks to which ViiV provides support funding. However, it does not sponsor clinical trials. She observed that collaboration with EDCTP is made more difficult by the complex contract negotiations and the limited funding.

Professor Peter Godfrey-Faussett, Senior Scientific Advisor with UNAIDS, briefly explained that UNAIDS is the UN's response to the global AIDS problem. UNAIDS is not a funding organisation. Its role is to harness the fruits of research in order to frame the UN's response to AIDS. The UNAIDS partnerships are with communities, politicians and other UN agencies (e.g. WHO). While science is important, it is also important to have initiatives which protect communities and research participants. UNAIDS is a committed advocate for HIV prevention. Collaboration with EDCTP is important because it creates links with the programmes, capacity and regulators of various countries.

Ms Siobhan Malone, Program Officer at the Bill & Melinda Gates Foundation. The Gates Foundation started collaborating with EDCTP in several HIV/AIDS projects early in 2006. In the past, there was limited collaboration with no large scale trials but that will change now. They have been looking at the intersection between HIV, family planning and infant mortality over the last two years. This could present opportunities for partnerships with EDCTP. The Gates Foundation is also interested in treatment optimisation and research on HIV vaccines, microbicides, circumcision, diagnostics, and combination treatments. Examples of other opportunities for future complementary collaboration include information sharing and train-the-trainers initiatives.

Dr Jimmy Whitworth, Head of International Activities at the Wellcome Trust, reported that the Trust is interested in HIV/AIDS and malaria research and on average funds 10 to 12 trials yearly. They are also interested in capacity building, global joint clinical trials and phase III/IV trials. He further observed that it is important to maintain links with EDCTP to ensure complementarity and avoid duplication.

Dr Brigitte Jordan-Harder, German Gesellschaft für Internationale Zusammenarbeit (GIZ: German Agency for International Co-operation). GIZ collaborates with EDCTP. There is much to be gained from such collaborations between research and developmental aid programmes since implementation of advances in research and local capacity building has to be embedded in the context of organisational change processes.

Comments

In the discussion after the presentations by the panel members the following points were raised:

- The clear message from the panel is about the need for collaboration. Perhaps EDCTP could act as a broker between the different funders with their different areas of interest, as this is not a role for scientists
- Networks: EDCTP has set up four regional networks in southern, east, west and central Africa to encourage partnerships between stronger and weaker institutes, thereby encouraging capacity building and joint projects
- In EDCTP2 it will be possible to have so called Participating States Initiated Activities; this increased flexibility will also contribute to capacity building
- With the funding instruments that will be available in EDCTP2, it will be easier to be flexible, particularly with timing; complementarity should improve
- UNAIDS has an interest in capacity building; it offers not scientific expertise but acts more as a facilitator/convenor to find answers for technical and methodological questions. For example, issues of ethics in prevention trials and the protection of human rights of individuals with AIDS are part of UNAIDS' remit
- UNAIDS and WHO have had joint meetings on methodology; this will be an important activity in the future. The Gates Foundation has also been involved in this; there will be a meeting soon to look at alternative trial designs
- Community capacity building for contraceptive options; consultation with communities is needed but also women themselves should be consulted.

Prof. Charles Mgone, EDCTP Executive Director, then summed up by saying that although there are many difficulties complicating collaboration, it is important that we come together to try and find solutions. EDCTP will have funding, with a known budget for the next 10 years and it has organised this and other stakeholder meetings to identify priorities. He

said that if we are going to create partnerships, we need to discuss these early in the process and put the plans into the EDCTP work programme. To deal with special issues, e.g. trial design, EDCTP will set-up expert groups either alone or in partnership. Capacity building is not just about training; it also involves infrastructure and systems development, as well as ensuring that the capacity built is used in an optimal way and is sustainable.

He concluded by saying that the meeting had highlighted the need for funding in many different areas that cut across the remits of the various funding bodies. For example, EDCTP cannot fund a global vaccine trial outside of Africa but it could create a partnership, early on, with other organisations which can fund activities in other areas such as Southeast Asia.

Prof. Helen Rees added that it is important to identify priorities and that we need to share ideas; it is good to have a dialogue. She said it was good to suggest partnerships for funding and it would help to know where to go to set up the partnerships. The proposal that EDCTP acts as a broker could be helpful. It would also be useful to streamline funding processes, e.g. the review of proposals. Information on how to access funding should be more readily available to researchers. She went on to say that we need more dialogue about capacity building. We should undertake mapping exercises to know what is available and where, so that capacity can be build more effectively. The regulatory issues are already being examined by EDCTP in partnership with WHO. Other issues such as human rights, ethics and adapted methodology need to be examined in partnership and through expert boards, etc.

Summary of recommendations

This summary brings together what has been recommended; the points made during the meeting are tentatively grouped. They illustrate

the whole spectrum of topics that were discussed and activities that were suggested for EDCTP to undertake. However, this list is not to be considered as a set of formal recommendations endorsed by the meeting participants.

Partnerships

- Importance of Good Participatory Practice (GPP)
- Guidelines for biomedical HIV prevention trials and community partnership
- Partnerships for priority setting: exchange information and involve communities as well as people in the field to identify priorities
- Promote empowerment: community education from African institutes for Africans
- Role of EDCTP with politicians and opinion leaders for advocacy:
 - Benefits of doing trials and studies
 - Raising human rights issues
 - Improving rights for MSM.

Capacity building

- Increase clinical trial capacity and have research sites and centres ready to recruit trial participants
- Capacity to perform pharmacokinetic and pharmacodynamic studies in the region; small local studies could accelerate time to market for products
- It is important to maintain existing laboratories, but there is a need for standardisation of practices. Better assays and laboratory standards are needed, not only for clinical development but also for post-marketing surveillance
- Safety surveillance networks
- EDCTP should continue field training
- Streamline capacity building between funders and African institutes
- Partners working together on joint activities such as development of guidelines.

Research ethics and regulatory affairs

- Regulatory activities for novel molecules and diagnostics
- Ethical issues are becoming increasingly complex, e.g. regarding placebo and standard of care
- WHO/UNAIDS partnership for ethics and methodological issues adapted to the needs of HIV/AIDS research in Africa.

Prevention

- Prevention: there is a need to establish and follow cohorts (e.g. from populations at high risk, or of exposed but uninfected children)
- Combination strategies for prevention: there is a need for innovative trial designs to test these efficiently. EDCTP has a role, but a multidisciplinary approach (e.g. with social scientists) is needed
- Critical appraisal of options B/B+ in the latest WHO guidelines in the setting of healthcare systems in Africa
- Need to accelerate assessment of the numerous microbicides and PrEP products in the pipeline
- PMTCT needs a systematic approach
- Need to improve the transition into adult services of HIV-positive children and adolescents
- Clinical trial designs using an open-label or standard-of-care comparator need to be explored as the standard placebo-controlled, double-blind clinical trial design is not always suitable for complex intervention strategies, such as combination prevention therapy
- Encourage the inclusion of adolescents and pregnant women in clinical trials for drug development and prevention strategies
- Involvement of social scientists in assessing the demand for prevention and, importantly, evaluating whether the available prevention strategies will be effective

- Research in specific at-risk populations to find the most suitable prevention strategies
- Assessment of risk perception and self-management
- Assessment of length of post-exposure prophylaxis; currently this is 28 days, but as infection occurs five days after exposure, this might be too long; shorter treatment could improve adherence.

Treatment

- Improved first-line treatments, especially for individuals (increasingly asymptomatic) who will stop and start treatment
- Determine the best time to start ART
- Paediatric drug formulations
- Better second- and third-line treatments
- Studies to find better formulations and dose-optimisation in order to minimise side effects; this could contribute to better adherence
- Better formulations and dose-optimisation for critical groups in clinical trials, e.g. pregnant women, women of child-bearing age and the increasing population of elderly HIV-positive individuals
- A diverse pipeline for products is needed as well as the development of different delivery technologies, reformulations, combinations of ART and non-ART products, and treatments that can be adapted to different settings and populations
- Determine how to treat co-morbidities, such as cancers and opportunistic infections
- More vaccines (prophylactic and therapeutic) at various stages of development and under investigation
- Improve understanding of mucosal immunity and the specificities of the vaginal environment
- Cure for HIV/AIDS research: aim to eliminate the HIV reservoir.

Health services research

- Health services research: how to improve treatment adherence, how to keep patients in care
- Development of improved diagnostics for monitoring treatment effectiveness and detecting resistance
- Reproductive health research: contraception, safe conception and the health of pregnant women
- Involvement of communities for implementation strategies
- During drug development it is necessary also to consider downstream aspects: how the product will be used, who will prescribe it and how safety can be monitored (e.g. in the case of adolescents and pregnant women who are often not included in the clinical development programme).

Annex 1. List of participants

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