



# HIV/AIDS research 1

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## Foreword

"HIV has spread worldwide in a short time, but is concentrated in low-income countries. In 2004, some 2.9 million deaths attributed to AIDS occurred in the low- and middle-income countries, compared with an estimated 22 000 in the high-income countries.

Sub-Saharan Africa is the region most affected by the epidemic. With only 10 percent of the world's population, it nonetheless accounts for 66 percent of all HIV cases and more than 75 percent of AIDS-related deaths. Countries in Asia and the Pacific do not have prevalence rates as high as those in Sub-Saharan Africa, but their populations are large and prevalence is rising. In 2004, approximately 505 000 AIDS-related deaths occurred in this region, representing about 17 percent of all AIDS-related deaths.

When the disease was first identified in the early 1980s, most of those living with HIV/AIDS were men. The proportion of women affected by the epidemic has steadily grown: by 2004, women and girls accounted for nearly 50 percent of all people living with HIV/AIDS, and in Sub-Saharan Africa, women and girls represent 57 percent of those infected.

Sexual intercourse accounts for approximately 80 percent of all infections. HIV is also transmitted via exposure to infected blood and from mother to child during childbirth or breastfeeding."

*Disease Control Priorities Project 2, 2006:*

*"HIV/AIDS presents an immense challenge to global health. However, globally, the quantity and quality of HIV/AIDS research is totally incommensurate with the unprecedented health, scientific, technological, social and political problems of the disease. Nowhere are research programs undertaking a comprehensive approach to HIV/AIDS. Europe, with its unique history and global responsibilities, and its strong economy, has the duty to create such a comprehensive research programme - and on a scale to match the scale of the challenge."*

Dr. Ismail Serageldin  
Chairman of EAGLES  
Director of New Library of Alexandria



“Europe is fiddling while the Third World dies. We need a global war on AIDS, in which we combine our best scientific intelligence and strategic thinking. There should be a Global HIV Enterprise, to contain the existing Global HIV Vaccine Enterprise, but also a new Global HIV Microbicide Enterprise, a new Global HIV Antiretroviral Enterprise – and a new Global HIV Public Private Partnership, to tap the strengths of industry.

And we should commit a few tens of billions of dollars to this, not the paltry few hundred million the world spends on HIV research and development now. We spend *trillions* of dollars on warfare to kill – surely we have to be able to commit a few tens of billions for a few years to *save* lives! If we could prevent AIDS we could save five million lives a year in the future. Wouldn’t that humanity defend us better from aggression and terrorism than any bombs?”

Dr. David McConnell,  
Co-Vice Chairman of EAGLES  
Smurfit Institute of Genetics, Trinity College, Dublin

“We sequenced the Human Genome in ten years. We have nearly defeated AIDS in the First World. So we know we can defeat AIDS in the Third World. Europe could lead the way by identifying developing and promoting the most appropriate intervention strategies”

Dr. Huanming Yang,  
Co-Vice Chairman of EAGLES  
Director, Beijing Genome Institute.



## Introduction

Thirty-nine million people have been infected by the HIV virus, and seventeen million have died as a result, mostly in the developing world. Nearly five million more are being infected each year. The pharmaceutical industry spends US\$1 billion to develop a product for conditions with much less impact – if there is a market. But for HIV/AIDS the people of the principal “market” have incomes of under \$1 a day. There are only two ways they can be cared for – by government institutions and academia taking the place of the industry, or at least paying for it to do what is necessary. Neither is happening on anything like a sufficient scale to tackle the extraordinary human and the scientific challenge of HIV.

HIV is a unique virus in human experience, devastating our immune system - which might otherwise present a natural defence; and transmitted in 80% of cases by a great human pleasure and biological necessity – sex. (Two other transmission routes are related: at childbirth, and through breast-feeding; the third is by needle-sharing in intravenous drug use.)

The immune system it attacks is highly evolved, complex and only partially understood. And the psychology and sociology of sexual behaviour might be said to be the same, varying enormously from culture to culture and almost always under a screen of discretion: we do not easily talk openly about our sex lives, or easily change our behaviour. Drug use is also hidden behind a veil.

The great challenge for Europe, with its long history of close involvement with the developing countries where the burden of HIV/AIDS is highest, in Africa, Latin America and increasingly in Asia, is – at sufficient scale - to investigate the quickest and most effective routes to ease the burden of sufferers and their families; to address with much greater vigour and intelligence the fundamental, practical and simply *managerial* problems facing the creation of effective vaccines, microbicial barriers, and new treatments, aiming to attract the brightest scientists and managers of a generation; and to complement and combine this work with related efforts elsewhere.



## The key recommendations

### Social and policy research: find and promote what works *now*

Perhaps the greatest challenge to effective global control of HIV/AIDS, is the lack of reliable evidence to guide the selection of prevention and care interventions for specific areas or populations.

In the same way that global policy makers increasingly recognize the need for rigorous evaluation of development programs to ensure their success and eliminate waste, the need for reliable scientific evaluations of AIDS control programs is equally paramount for the same reasons.

Lack of data on both the effectiveness and the cost of interventions to guide informed policy-making means that the current allocation of resources for HIV/AIDS prevention is frightening rare evidence-based.

The greatest research challenges for making immediate improvements in care and treatment for developing countries concern how to adapt care and treatment strategies to low-income, low-technology, low-human resource capacity settings in ways that maximize adherence; minimize toxicity, monitoring, and cost; and maximize the prolongation of high-quality life from ART—all without damaging the existing and often fragile health care infrastructures.

Specifically EAGLES recommends:

#### 1. Establish a unified European response adequate to the size of the problem.

AIDS is devastating Africa and SE Asia and Central Eurasia, yet the international responses are weak and disproportionate. European responses suffer further from excessive fragmentation (notably between member States). As in so many other matters there is no strong *European* programme on HIV/AIDS. There is an urgent need to mobilise European science

on a large scale to combat HIV/AIDS.

The EC should take the initiative in developing a unified *European* HIV Research Programme for Developing Countries. This should be funded partly by the EC budget and partly by Member States budgets. It should be run by an organisation modelled on the European Research Council (ERC). It should be given responsibility for a ring-fenced HIV programme of grants for fundamental and applied research which would be large and awarded just on excellence. Grants could be awarded to scientists in public and private institutions on the basis that all results will be published. It would have the capacity to form public private partnerships focused perhaps on translational research, production systems and clinical trials.

#### 2. Comprehensively evaluate interventions

Comprehensive evaluation and systematic comparison of all HIV/AIDS interventions, across cultures and countries, including identification of research and development (R & D) strategies that would bring benefit to the greatest number in the shortest period of time. In particular, issues of condom use and for practical reasons very importantly and widely neglected pre-, peri-, ideally, post-coital antiretroviral interventions in control of individual sexual partners or/and iv drug users and access to these substances as well as to treatment require effective full-scale investigation.

#### 3. Get objective, incontrovertible evidence on condoms

According to Wiwat Rojanapithayakorn, HIV/AIDS Team Leader, World Health Organization China, Beijing, China, "one of the main reasons for the rapid spread of HIV in Asian countries is the massive transmission among sex workers and clients. One solution in the commercial sex business is said to be the "100% condom use programme". Since its conception in 1989, this programme has been implemented in Thailand, Cambodia, Philippines, Viet Nam, China, Myanmar,



Mongolia and Laos, with variations in programme components between countries. The principle is to promote "No condom - No sex" in all types of sex work. According to WHO, "the 100% condom use programmes in Thailand and Cambodia, which are being implemented on a nationwide basis, are the main reason for the decline in the HIV epidemic" in those countries.

Europe needs to provide thorough, irrefutable evidence regarding the effectiveness of this programme, including objective analysis of any weaknesses – such as the inability of many women to negotiate condom use - and present and communicate its results clearly and dispassionately to policy-makers internationally. This needs to be done in the face of strong opposition on the basis of ideology from several groups and countries both within and outside Europe. This is already a very accepted strategy and so well implemented in many areas that Europe cannot play a leading but only a strongly supporting role.

Another need comes from mobile societies where partners may take temporal or seasonal work away from home. Home-based partners often cannot insist on condom use upon return of the partner. Because of the not very encouraging first data from classical microbicide applications trials (enhancing!) novel concepts such as carefully selected and/or local (ie intra vaginal) application of a pulse (one shot) of ie delayed release of ARV substances has the same high profile protective potential as pre intervention single high dose Antibiotics to surgical interventions while minimizing generation of resistant mutants.

#### **4. Solve the access problem**

Most people who could benefit from available control strategies (including treatment) do not have access to them. Modeling of the epidemic has determined that existing interventions could prevent 63 percent of all infections projected to occur between 2002 and 2010. However, as of now, fewer than one in five people at high risk of infection have access to the most basic prevention services, including

condoms, AIDS education, mother to child transmission (MTCT) prevention, voluntary counselling and testing (VCT), and harm reduction programs. Europe must use social and policy research to investigate why, and by what means access could be increased.

#### **5. Find the best palliative care packages**

Despite the wide range of interventions to treat symptoms in people living with HIV/AIDS and their low cost, the need for palliative care for such people is far from being met. The lives of people infected with HIV/AIDS can also be greatly improved and prolonged through psychosocial support, treatment of opportunistic infections, ART, and palliative care, which includes not only end of life and pain control, but also the psychological, social and spiritual problems of patients and their families. End-of-life care can be provided in hospitals, hospices and individuals' homes. Many inexpensive measures to treat pain, diarrhea, nausea, and skin conditions in infected individuals are available and can improve patients' quality of life. Micronutrient supplements, which only cost US\$15 a year, can increase body weight, reduce HIV viral load, improve CD4 counts, and reduce opportunistic infections in infected individuals. Europe should support research to determine what palliative care works best, and is most cost-effective, in different settings.

#### **6. Help children**

An estimated 2.3 million children were living with HIV/AIDS at the end of 2005, 2 million of them in sub-Saharan Africa. Most of these children acquire HIV from their HIV-infected mothers during pregnancy, birth or breastfeeding. With successful interventions the risk of mother-to-child HIV transmission can be reduced to 2%. However, such interventions are still not widely accessible or available in most resource-limited countries where the burden of HIV is highest, and an estimated 1 500 children get newly infected with HIV each day. Without HIV care, including antiretroviral



therapy, the progression of HIV infection in children is particularly aggressive. In 2005, an estimated 380 000 (290 000–500 000) children died of HIV-related causes. It is likely that one half of them did not live past their second birthday. In hard hit countries such as Botswana and Zimbabwe, HIV is the underlying reason for more than one third of all deaths among children under the age of five.

Not all the antiretroviral drugs approved for use in adults with HIV exist in an appropriate form, or are licensed and approved, for use in children—and those that are available often are unaffordable. Syrup formulations of antiretroviral drugs have been developed, but they tend to be foul-tasting, must be taken in large volumes, require refrigeration and have short shelf lives once opened—all of which can make them impractical. Fixed-dose combination drugs, in which two or three different drugs are combined in a single pill to simplify treatment regimens, show excellent clinical, immunological and virological results when used in adults. Yet few such drugs are available currently for treating children.

Research is needed to investigate why these children are not receiving appropriate treatment, and to create solutions to this problem.

### **7. Develop positive results on circumcision**

In a series of recent publications, it has been shown that male circumcision reduces the rate of infection by the virus by 60%. The implications of this result for women as well as for men, for practical prevention programmes - and for changing sexual behaviour - now need to be thoroughly explored.

### **8. Face squarely the role of sex workers in HIV transmission**

In every culture there are sex workers, both casual and professional, and usually their

activities are treated as taboo. Some major HIV/AIDS aid programmes even forbid providing them with any assistance. Yet it is clear they play a major role in community transmission of HIV. Their role in both transmission and potential prevention needs to be clearly identified in each country and culture, with objective evidence that policy-makers and aid programmes cannot ignore.

### **Vaccine and microbicide research: think brilliantly – and industrially**

If there were an effective vaccine delivered to those most at risk, or a simple effective preventative measure that a woman most at risk could use before sex, what a difference it would make! The HIV/AIDS epidemic could be halted in its tracks. But HIV is a very difficult virus, attacking the immune system itself, and while significant progress is being made, the challenge remains enormous - and must be tackled at more than a token level of commitment.

This means investing properly in brilliant research, in new ideas, and in development: but it also means Europe putting an industrial scale of commitment and energy in turning new results and ideas into working products. In brief, it means thinking industrially - like a company eager to make a profit, but here eager so save tens of millions of lives - and bringing the expertise of the best possible management into the loop. This is not a game for bureaucrats alone.

For example, policy-makers may be unaware that to take a new construct from a university laboratory bench to a clinical trial, even simply to Phase I, has become a major undertaking in terms of time, money and sheer commitment.

Regulatory barriers are high, expensive and time consuming. Even a five-year programme grant is unlikely to give sufficient time for a new construct to be developed and optimised in vitro, to be subjected to immunological testing in animals, to be produced under current good



manufacturing practices (cGMP), to be studied for toxicology, to have regulatory documents written, insurance arranged, trial sponsorship ensured and then to have the clinical trial itself organized and managed.

Furthermore, even large research councils or charities balk at the size of the awards necessary to cover these activities, and move from science to the clinic.

The European Commission itself acts under enormous constraints. Politically, it is driven by member states to support broad and intense activity across the whole field of HIV/AIDS research, throughout Europe – but it is not given sufficient resources to the job. It has made a valiant attempt to do so, but the inevitable consequence is that nothing can be supported in sufficient depth.

Under the European Commission's Framework Programme Five (FP5), the EuroVacc consortium was funded to develop candidate HIV vaccines and to take these to Phase I trials. This was accomplished, albeit after delay, but it has proved impossible to fund these constructs further as the expense is considered too high.

Another glaring example of resource constraints is the European Developing Countries Clinical Trials Programme (EDCTP), which will fund capacity building and clinical trials, but a recent agreement with the Bill and Melinda Gates foundation for vaccine trials in Africa has placed a ceiling of €4m on each award – perhaps 20% of the likely cost of the most urgently needed Phase I/II studies in an at-risk population.

Again, funding for vaccines and microbicides in FP6 has effectively been forced to focus on coordination rather than new products, as this is a cheaper option and more deliverable than genuine support to take new constructs to clinical trial.

The failure of member states to fund European projects in sufficient depth is also illustrated by the European Microbicides Project (EMPRO). EAGLES would be pleased

to think that new products were to arise out of this project; however, the UK's MDP (Microbicides Development Programme) – which has a clinical programme from DFID (Department for International Development) and the UK MRC (Medical Research Council) with funds amounting to £42m (€62m) over 2001-2009 – has not yet been approached to take any EMPRO products to trial in Europe or in Africa.

In reality, we face the double global challenge of both the basic research and the lack of political and financial support to proceed efficiently to the clinic, in a well-managed, comprehensive, industrial scale programme.

### The challenges of vaccine science

Far more research is needed. At the scientific level, more than 30 candidates are in small-scale trials, but the candidates are very similar to each other. Nearly all are based on the hypothesis that a vaccine can confer protection by eliciting a cell-mediated immune response. The cell-mediated hypothesis is just beginning to be tested in large-scale trials, and results are not due until late 2007 at the earliest. If the basic hypothesis is proven unworkable, the pipeline of candidates will be rendered mostly irrelevant.

Among vaccines, envelope-based subunit vaccines (AIDSVAX) developed by VaxGen have failed to induce neutralising antibodies in two different efficacy trials. There are only two T-cell vaccine candidates that currently have funding for Phase II/III study: the Merck and US NIH (National Institutes of Health) VRC adenovirus vectors. In addition, there is sanofi pasteur's ongoing Phase III trial in Thailand, designed to assess the efficacy of an avian poxvirus construct (ALVAC VcP2501) expressing several clade E genes, boosted with VaxGen clade M/E subunit vaccine.

This is not a failure of vaccine research, against the extremely difficult target of HIV – it's a failure of the *volume* of research and development, and the encouragement of



new ideas, that is needed to achieve the goal.

As a result, strong alternative hypotheses have been largely neglected.

The *first* is that an effective vaccine should elicit a broadly neutralizing antibody immune response. None of the candidates in trials elicits this response.

A *second* and still under-funded hypothesis is that an effective vaccine must elicit immune responses in the mucosal linings of the genitalia, given that HIV is most often transmitted sexually. In Europe, MUVAPRED is investigating this, but the challenges are enormous and the scale of the enterprise needs to be widened and expanded.

A *third* avenue that deserves more attention is to understand why live-attenuated AIDS vaccine candidates have shown protection in monkeys that is better than any other type of candidate. Although current live-attenuated candidates cannot be used in humans because there is a safety risk that they will cause HIV infection, researchers should try to understand the mechanism by which live-attenuated candidates work. With this insight they may be able to design candidates that achieve the same effect safely.

For many of the vaccine candidates now in trials, the process for manufacturing them is slow, expensive and, in a few cases, just not feasible on a large scale. Little is being done to engineer better manufacturing processes.

Vaccine candidates are also advancing through small-scale trials without global consensus about how to assess which ones are most deserving of large-scale trials. And in most developing countries, there remains little capacity to conduct large-scale trials. Europe's programme for this, the EDCTP, has been severely criticised in the past for its slow rate of progress.

EAGLES supports the recommendations of the International AIDS Vaccine Initiative (IAVI) and the Global AIDS Vaccine

Enterprise that *global research consortia* need to be created to solve key problems.

However EAGLES also notes that in the past the best progress has been made when research groups have been given both sufficient funding and time to allow constructs to be fully developed and tested. This has either occurred in industry, or where there has been strong government or international support for a project over a considerable period of time.

EAGLES therefore recommends that Europe create project funding in sufficient depth and duration to allow products to be completely developed, and to allow peer-review to determine which to support. A second round of funding would then be required to take the most promising candidate further. This would allow European integration, as the funding would drive coordinated decision-making.

EAGLES also strongly supports the still unimplemented, thorough and precise proposals by leading HIV/AIDS researchers and coordinators from throughout Europe for a 'European Union Action Plan for HIV Vaccine Development' (May 2004). The authors clearly identified the weaknesses of existing European HIV Vaccine activity, and made fundamental proposals for practical action. Among these the leading element is the need for the transformation of Europe's HIV vaccine research and development 'system' into one that worked with a project-oriented, industrial vision, rather than the present rather academic, competitive milieu under weak coordination and weak management. Within it, such a vision clearly required the creation and efficient management of many more clinical trials, to take Europe's growing number of strong vaccine candidates to the point of genuine discovery of their usefulness.



*In brief, to create a real and effective HIV/AIDS vaccine Europe needs to:*

### **1. Urge member states to double resources, both financial and human, to match the scale of European ability and ambitions.**

It is one thing to ask the Commission to fund across the whole spectrum of HIV/AIDS research, Europe-wide; it is quite another for member states to recognize and commit the scale of resources that must be devoted to these goals for them to be more than wishful thinking.

Global spending on vaccine research and development should at least double, to US\$1.5 billion annually.

### **2. Test today's ideas - through manufacturing up to phase III trials.**

Europe should link fully with the Global HIV Vaccine Enterprise to prioritize the pipeline of 30 similar candidates now in small-scale trials, using standardized laboratory techniques and benchmarks.

The best candidates should be funded to advance to large-scale trials in developing countries and other areas where the incidence of HIV is high, and where protection against a diversity of HIV subtypes can be evaluated.

[The Global HIV Vaccine Enterprise is an alliance of agencies working toward an AIDS vaccine. Patterned after the Human Genome Project, the Vaccine Enterprise is intended to foster collaboration and coordination across research and development programs. It was proposed by the Bill & Melinda Gates Foundation and others in a June 2003 paper in the journal *Science*, and endorsed by the heads of the G8 nations at their summit in June 2004.]

In determining which candidates are most promising, feasibility of manufacturing should be considered. Greater attention needs to be given to improving

manufacturing processes. New facilities will be needed to supply vaccine candidates for more small and large trials.

### **3. Design tomorrow's ideas.**

Intensified research is needed to design new vaccine candidates, focusing on three areas:

*First, vaccine candidates that elicit a broadly neutralising antibody immune response and long-term T-cell memory need to be designed and tested.*

*Second, researchers should work to understand the mechanisms by which live-attenuated candidates elicit protection in monkeys.*

*Third, candidates that elicit mucosal immune responses need to be researched, designed and tested on a sufficient scale.*

The immediate goal is to design candidate vaccines that cause the immune system to produce protective responses from both of its major arms — cellular immunity and neutralising antibodies. Europe's AIDS vaccine integrated project plays an important role here, but on a small scale given the global threat.

There are major challenges to discovering vaccines capable of eliciting both types of responses. While researchers have developed vaccine candidates capable of eliciting cellular immunity against HIV in animal studies, early data from clinical trials suggest that the responses in humans may not be sufficiently potent, and current candidate vaccines may be duplicative if not significantly optimised. In addition, while researchers have identified antibodies that can bind to and neutralize HIV, they have been unsuccessful in designing vaccine candidates to elicit those antibody responses.

To fill gaps in scientists' understanding of the interplay between HIV and the immune system, large-scale immunomonitoring and virological studies should be conducted of people who have very recently become



infected with HIV, to learn important information about the role of a vaccine in the initial stages of infection.

#### **4. Build capacity rapidly for large-scale trials in developing countries.**

We need regional AIDS vaccine trial centres, each capable of conducting multiple large-scale human clinical trials. These centres should be in the areas where most new HIV infections are occurring, and different subtypes of the virus are circulating. This includes developing countries in Africa, Asia, Eastern Europe and Latin America.

Establishing capacity involves constructing clinics, outfitting laboratories, hiring and training staff. It may require improving local utilities and health care infrastructure, particularly programs that provide HIV/AIDS-related services. It necessitates building political and community support. Europe can accelerate vaccine development by providing incentives for the private sector to pursue an AIDS vaccine.

#### **5. Enact public policies to facilitate vaccine development and prepare for access to a future vaccine.**

Europe can help accelerate vaccine research and development by enacting policies that provide incentives for the private sector to pursue an AIDS vaccine.

Regulatory agencies in Europe should provide assistance to their counterparts in developing countries in reviewing and approving clinical trials of vaccine candidates. The public sector must lead in preparing for access to a future vaccine. Typically new vaccines take up to 20 years to reach developing countries after their introduction in industrialized countries. Europe can avoid access delays by planning ahead—for purchasing, manufacturing and distributing the vaccine to meet global demand.

## **The challenge of microbicide science**

The term 'microbicides' refers to a range of new products that would share one common characteristic: the ability to prevent the sexual transmission of HIV and other sexually transmitted diseases (STDs) when applied to mucous membranes, in particular those of the vagina. A microbicide could be produced in many forms, including gels, creams, suppositories, films, or as a sponge or ring that releases the active ingredient over time.

Today's prevention options - condoms, mutual monogamy, and STD treatment - are not realistic for millions of people around the world, especially women. Many women do not have the social or economic power necessary to insist on condom use and fidelity or to abandon partnerships that put them at risk. Because microbicides would not require a partner's cooperation, they would put the power to protect into women's hands.

At least five international scientific meetings have concluded that microbicide development is both necessary and feasible. Most recently, the Rockefeller Foundation convened a high level panel of scientists to evaluate the field and identify opportunities for accelerating microbicide science. The Scientific Working Group of the Rockefeller Initiative concluded in its report *The Science of Microbicides*:

*Accelerating the development of microbicides is a realistic and important near-term opportunity. The challenges facing microbicide development are well understood and manageable. The first generation of microbicide products is now undergoing clinical testing, and, if effective, should be on the market well within this decade. Subsequent product generations will deliver improved effectiveness, a broader spectrum of activity, and enhanced acceptability for consumers.*

Nevertheless, as for vaccines, HIV remains a difficult target, and EAGLES considers that the sheer volume of research and development needs to increase significantly



to achieve the goal of an effective microbicide in a reasonable time. For example, the first generation attempt (detergent spermicide N9) failed at Phase III; four current Phase III trials are all testing one concept, inhibition of HIV binding; and there is funding for only two future Phase III trials of antiretroviral agents.

Globally, more than 60 products or compounds are under research- but this is not enough in itself. The number and ingenuity of the candidates needs to be increased, and even this research will go to waste - unless that "industrial" scale and commitment is present, and sufficient funding, resources and management are committed for large-scale clinical trials of the leading candidates. Ultimately it is only in clinical trials that we learn what works and is safe in human beings.

In Europe, the European Microbicides Project (EMPRO) aims to develop microbicides that are better than, or synergistic with, existing approaches. EMPRO believes it is taking some quite novel approaches in its design of new molecules and some of the technologies that will be utilised include nanocluster, nanobody and anticalin scaffold technology. EMPRO partners will generate a significant number of new molecules that will be screened in the laboratory, not only for their effect on HIV but also for their effect on the natural microorganisms present in the vagina and on the vaginal epithelium. EMPRO will also investigate how well their new candidate drugs work in combination with each other or in combination with other drugs developed outside the project.

The results from the initial laboratory testing will help to determine which candidates move through to the next step of development. However, other factors also need to be considered as drugs move forward in development. These include whether the drug is better than existing drug, how easy it is to manufacture, how easy it is to formulate, how long it will take to develop, what regulatory hurdles there may be, how stable the drug will be, what

the cost is likely to be, whether use of the drug is likely to generate drug resistant HIV, and how safe and effective the drug is.

Taking all these into consideration, EMPRO will select microbicide drug candidates based on the best available scientific evidence, in line with the principles of rational drug development and in context with the global microbicide effort. The best candidate(s) generated by EMPRO are expected to enter into clinical testing in the later stages of the project.

EAGLES recommends that the potential benefits of these innovative ideas greatly outweigh their cost, that funding for EMPRO and related projects should be doubled, and sufficient consideration be given to the resource implications of the ultimate need for large-scale clinical trials.

### The challenge of resistance and novel ARTs

Resistance to existing antiretroviral therapies (ARTs) is increasing, and can be predicted to rise further, particularly where drugs are only available intermittently or not taken on a regular schedule. Resistance needs to be monitored carefully in developing countries, where Europe needs to provide support to create *in-country laboratories* that can offer effective resistance monitoring facilities.

Meanwhile pharmaceutical companies have been relied on to develop new ARTs, but the future growth in the market is in poor communities in the poorest countries, and is little incentive to these companies. Europe therefore needs to support and develop new incentives for new ART development, both in academia and in industry. In the process it must prepare itself to act, in effect, like a public-private partnership (PPP), working in partnership with existing companies where this is beneficial to both, in the interests of creating effective manufactured products to deal with what has become one of the greatest and most tragic scourges of the developing world.

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