Long-term effects of HIV treatment in sub-Saharan Africa: from access to quality

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Research in action: from AIDS to global health to impact.
A symposium in recognition of the scientific contributions of Professor Joep Lange.

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Antiviral Therapy
SUMMARY

On Tuesday 14 October 2014, 850 family members, friends, colleagues, prominent scientists and dignitaries from all over the world gathered in Amsterdam to pay tribute to the lives and legacies of Joep Lange and Jacqueline van Tongeren. The remembrance was held at the Amsterdam Medical Centre (AMC) where Joep and Jacqueline met and worked together for many years. The day was organized by the AMC, the Amsterdam Institute for Global Health and Development (AIGHD) and PharmAccess Foundation. The latter two were both founded by Joep. A morning symposium titled ‘Research in action: from AIDS to global health to impact’ highlighted Joep’s scientific legacy (Figure 1). During the remembrance in the afternoon, a range of speakers shared memories of Joep and Jacqueline. As was the case during their lives, the personal and the professional were closely intertwined throughout the day. As Prof Peter Piot said, Joep and Jacqueline shared a common perspective on life: ‘La folie suprême est de voir la vie comme elle est et non comme elle devrait être.’ If there was one thing that defined them both, it was indeed that they saw life – and lived it – not as it was, but as it should be.

Figure 1. Morning symposium.
Photo by Rebke Klokke.
‘Joep’s place in history is really as the visionary architect of combination therapy,’ Prof Piot stated, adding that ‘it cannot be stressed enough that he was ahead of his time, a true innovator.’ Joep’s contribution didn’t stop at science. Dr Khama Rogo of the World Bank explained that ‘it’s not enough to be a doctor or a researcher if you’re not also an activist.’ Joep fully understood the importance of translating research into action and generating impact for people. Prof Marcel Levi, chairman of the AMC, summarized the enormity of the impact Joep had on the world with the words ‘it’s rare to know someone who has saved millions of lives.’

The scientific symposium traced Joep’s career, starting in the early eighties with the treatment of the first AIDS patients and the design of antiretroviral therapy, moving towards the emerging field of global health and ending with his most recent focus: using knowledge derived from scientific research to improve access to quality health care in real-world settings. From Prof Françoise Barré-Sinoussi, who won the Nobel Prize for the discovery of HIV, to Prof Michael Merson, who founded Duke University’s Global Health Institute, the list of presenters reads like a who’s who of people involved at key moments in the history of HIV and global health (Figure 2). ‘And Joep,’ as Barré-Sinoussi said, ‘contributed to all eras of HIV.’

More memories of Joep and Jacqueline shared throughout the day are available at http://www.joepandjacqueline.org/remembrance/.
RESEARCH IN ACTION: FROM AIDS TO GLOBAL HEALTH TO IMPACT.

The morning symposium served as a platform to recognize Joep Lange’s scientific achievements and to pay tribute to his activism in the field of HIV treatment and global health. It was also an occasion for colleagues to share their feelings and personal anecdotes about working with Joep.

Joep’s friend and colleague Prof Peter Reiss of the University of Amsterdam opened the symposium, welcoming attendees and encouraging the audience to once again be inspired by Joep’s work and to continue his legacy into the future.

A word from the co-chairs
Peter Reiss introduced the two co-chairs of the symposium, Prof Michel Kazatchkine and Dr Debrework Zewdie.

Prof Michel Kazatchkine shared his memories of Joep as a man who ‘was convinced of the power of science to build knowledge and then translate it into action.’ Kazatchkine emphasized Joep’s generosity, compassion and tolerance, all qualities that are considered essential for a good doctor. Qualities, Kazatchkine added, that Joep fully shared with Jacqueline. While Joep was a tolerant man, he would never accept a policy that wasn’t evidence-based. Joep fought for equity, for the right of everyone to access and enjoy the advancements of science.

Dr Debrework Zewdie began by saying that ‘Joep was born a Dutchman, but became a global citizen who felt that the fruits of science should be shared by everyone.’ For example, the yearly International Workshop on HIV Treatment, Pathogenesis and Prevention Research in Resource-Poor Settings (INTEREST), nicknamed ‘the African CROI’, provides young African researchers with the opportunity to present their data in the presence of established scientific leaders and to learn from this experience. ‘I was amazed by Joep and Jacqueline’s work in building African scientists and shepherding the INTEREST group. Now, it is up to us to step in and make sure to continue what they started.’

The co-chairs introduced the subsequent speakers, who each touched upon different aspects of Joep’s career as a scientist and activist.
Peter Reiss is Professor of Medicine at the AMC in Amsterdam in the Division of Infectious Diseases, the Department of Global Health and the AIGHD. He was recently appointed Director of the Netherlands HIV Monitoring Foundation, and serves on several Scientific Advisory Boards.

Debwerk Zewdie is a clinical immunologist by training and has spent the last 30 years on research and development work including managing development programmes at country, regional and global levels. She worked for the World Bank and the Global Fund.

Michel Kazatchkine is the UN Secretary General’s special Envoy on HIV/AIDS in Eastern Europe and Central Asia. Previously, he was Head of the French Agence Nationale de Recherches sur le Sida, France’s Ambassador on AIDS and Executive Director of the Global Fund to Fight AIDS, Tuberculosis and Malaria.

David Cooper is Scientia Professor of Medicine at the University of New South Wales, a Fellow of the Australian Academy of Science (FAA), and Director of the Kirby Institute for Infection and Immunity in Society based at UNSW Australia.

Francoise Barré-Sinoussi was awarded the Nobel Prize for Medicine 2008 and is Director of the Regulation of Retroviral Infections Unit, Department of Virology, Institut Pasteur. She is involved in retrovirology research and is particularly recognized for the discovery of HIV.

Menno de Jong is Professor of clinical virology and head of the Department of Medical Microbiology at the AMC. Joep Lange recruited him as a trial physician and supervised his PhD research on the causes and implications of HIV treatment failure in 1996.

Michael Merson is the founding director of the Duke Global Health Institute. He is Vice President and Vice Provost of Global Strategy and Programs and Vice Chancellor for Duke-National University of Singapore Affairs at Duke University.

Eric Goosby served in the US State Department as Ambassador-at-Large and US Global AIDS Coordinator, overseeing the implementation of the President’s Emergency Plan for AIDS Relief (PEPFAR). He is Director at the Institute for Global Health Delivery and Diplomacy, University of California, San Francisco.

John Simon has been US Ambassador to the African Union and the Executive VP of the Overseas Private Investment Corporation. He served on the National Security Council staff, White House, and as Deputy Assistant Administrator, US Agency for International Development. He is a Founder/Managing Partner of Total Impact Advisors.

Fola Laoye is Chair of Hygeia Nigeria Limited. She has an MBA from Harvard Business School and qualified as an Associate member of the Institute of Chartered Accountants of England and Wales in 1995 and of the Institute of Chartered Accountants of Nigeria in 1997.

Khama Rogo is Lead Health Sector Specialist with the World Bank and Head of the World Bank Group’s Health in Africa Initiative. Prior to this, he taught Obstetrics and Gynaecology at the University of Nairobi and was President of Medical Affairs Africa for Ipas.

Onno Schellekens is the Managing Director of PharmAccess, an organization founded by Joep Lange, which is dedicated to improving access to affordable quality health care for people in sub-Saharan Africa.

Figure 2. Speakers and chairs.
ARV therapy: past, present and future

It is hard to imagine robust economic growth where so many adults are dying in their productive prime, leaving the very young and the very old to cope alone.’

Economist, 12 August 1999.

Prof David Cooper took the audience back to the 1980s when he, like Joep in the Netherlands, was confronted with the first AIDS cases in Australia [1–6]. Cooper detailed the important findings made by Joep that plasma levels of viral protein P24 (a then proxy for viral load) were predictive of the stage of HIV infection, with low P24 in the absence of symptoms and high P24 in symptomatic AIDS patients [7]. In addition, Joep was involved in important research on syncytium-inducing versus non-syncytium-inducing viruses, with the latter being more virulent [8].

Later on, the molecular basis for this phenomenon was found with the discovery of the secondary receptors for HIV – the chemokine receptors. Non-syncytium inducing viruses are CCR5-tropic while syncytium inducing viruses are CXCR4-tropic, with implications for prognosis [9]. Cooper provided examples of the first clinical trials of antiretroviral therapy that failed due to a transient response related to the development of drug resistance: AZT monotherapy, AZT+3TC dual therapy and NVP-AZT alternating therapy [10–12]. These trials convinced Joep that only triple therapy would be the way forward to prevent drug resistance, as revealed by the successful INCAS trial that tested the triple therapy combination of AZT, ddI and NVP, published in JAMA in 1998 [13]. Triple therapy remains the cornerstone of HIV treatment today and is now scaled-up to provide increasingly early treatment which reduces the risk of ongoing HIV transmission [14–17].

Together with Prof Cooper and Prof Praphan Phanuphak, Joep initiated the HIV Netherlands Australia Thailand Research Collaboration (HIV-NAT) in Bangkok in 1996 to build research capacity in Thailand in the field of HIV treatment. To date, HIV-NAT encompasses 112 staff and runs long-term studies involving over 2,000 adults and children on antiretroviral therapy.

Cooper observed that Joep was lately returning to his original passion and was involved with various efforts toward a functional cure for HIV. Referring to the continued spread of HIV, Cooper emphasized the thoughts of Joep’s favourite economist JF Rischard that ‘we are facing a problem of immense complexity, which is getting out of hand in an exponential way. The traditional way of working along a linear time scale
will not be able to cope with this.’ In addition, he sketched how Joep understood that HIV/AIDS seriously hampers economic growth in many developing nations, and the ensuing need for a concerted global effort, a broad coalition of the public and private sectors, civil society and academia, with clear divisions of tasks and accountability. In his conviction that ‘what works’ should prevail over the notion of what constitutes an ‘ideal society’, Joep often quoted Martin Wolf: ‘The sight of the affluent young of the west wishing to protect the poor of the world from the processes that delivered their own remarkable prosperity is unutterably depressing.’ He saw sustainable financing of health care for the masses, not necessarily through the public sector, as a prerequisite for a future without donor dependence.

Cooper ended his talk with what he described as Joep’s legacy: ‘As there is no vaccine or cure right now, antiretroviral therapy is our major intervention. It would be a tragedy if we fail to get enough people on treatment to reduce incidence and we need to persuade civil society that flat lining of funds is just plain unacceptable. We MUST finish the job.’


Towards an HIV cure

*Joep contributed to all eras of HIV.*

Prof Françoise Barré-Sinoussi.

Subsequently, Nobel Prize laureate Prof Françoise Barré-Sinoussi, co-discoverer of HIV [18], acknowledged Joep’s long-term commitment to find a cure and referred to how he was also an advocate for a global scientific strategy: joining forces in an international working group to define the main research priorities and coordinate research efforts. ‘The time to accelerate HIV research is now.’ Prof Barré-Sinoussi emphasized the need for basic science for HIV vaccine development and HIV cure. She highlighted that the formation of viral reservoirs immediately after primary infection is very rapid: even if only one out of 1.7 billion CD4 T-cells is infected, a viral rebound is possible [19]. In order to work towards a cure, it is important to learn more about the properties of latently HIV-infected cells and how viral re-activation pathways can be influenced [20].

In her presentation, Barré-Sinoussi considered complete eradication of HIV in an infected patient (sterilizing cure) less likely than putting HIV into remission (functional cure) [21]. Working towards a functional cure was one of Joep’s most recent topics.
of research in Amsterdam. New research that was taking place at AIGHD under his supervision may lead to a potential breakthrough in the treatment of people with HIV. New insights suggest that immediate treatment of a newly contracted HIV infection can be so effective that it may be possible to effect a functional cure. This would mean that after some time, treatment can cease and the virus will no longer be detectable in the patient’s blood. The virus, which would still be present in certain parts of the body, would be so weakened that disease progression would come to a halt and HIV would no longer be transmissible.


From HIV to emerging infectious diseases

‘Be creative and think big to tackle the real problems.’

Prof Menno de Jong recalls how Joep taught him to approach his research.

Prof Menno de Jong started his presentation by recalling how Joep had been his mentor, friend and inspiring colleague. One of the things that Joep felt strongly about was that there was no point in research for research’s sake, but that it should always have the aim to generate impact in real-world settings. De Jong then drew a parallel between HIV and his current professional field, explaining that ‘we can apply the lessons learnt from HIV to other emerging infectious diseases like influenza and Ebola.’ Mirroring aspects of HIV treatment, the concept of triple therapy has proved promising against H1N1 influenza infection in immune-compromised children [22]. He provided an overview of the important emerging infectious diseases during the past decade, all of which are transmitted from animals to humans (2003 SARS-CoV, 2004 H5N1 influenza, 2009 H1N1 influenza, 2012 MERS-CoV, 2013 H7N9 influenza and 2014 Ebola virus).

One common denominator with HIV is that the emergence of new pathogens usually takes place in regions of the world where the infrastructure and the human capacity to recognize and contain such outbreaks are the lowest [23]. De Jong explained that the early recognition and containment of infectious diseases requires, among other things, laboratory and research capacity. While the importance of building laboratory capacity in Africa is being increasingly recognized, there is much room for improvement. For example, more optimal use could be made of the opportunities for cross-fertilization between research and laboratory capacity in Africa, both in terms of HIV and other important infectious diseases.
According to De Jong, clinical research responses to infectious disease outbreaks are usually fragmented and often too late. There are global regulatory hurdles for timely clinical research during epidemics and as such, important opportunities for gathering essential data in the early stages of an outbreak are often missed. The average time that passes between the development of a clinical research protocol and the recruitment of the first patient, De Jong said, is far too long. Needless to say, an epidemic doesn’t wait for paperwork. He argued that it is crucial to develop pre-approved standardized open-access clinical research protocols, translated in many languages, to react as swiftly as possible in case of disease outbreaks. ‘We need a new paradigm, we need to be prepared and ready to act.’


**From HIV to global health**

*Joep leaves behind a legacy of leadership, vision and always striving for a healthier tomorrow.*

Prof Michael Merson.

In the early 1990s, Prof Michael Merson hired Joep as Chief of Clinical Research and Drug Development for the World Health Organization’s Global Programme on AIDS. It was in this capacity that Joep made his first trip to Africa, which proved to be a life-changing event for him. In the course of their careers, both Merson and Joep moved from HIV research to global health, which has been defined as ‘the area of study, research and practice that places a priority on improving health and achieving equity in health for all people worldwide.’

In his presentation, Merson outlined five key ways in which HIV research contributed to the relatively new discipline of global health [24]. First of all, HIV was the first post-modern pandemic that affected populations globally in both low- and high-income settings. Second, HIV fostered new collaborative approaches, such as the treatment–prevention model. This method highlighted the importance of multidisciplinary approaches to prevention and care, which has become a hallmark of global health research. Third, HIV led to a global advocacy movement in which scientists joined forces with human rights and other activists to fight stigma and demand better treatment. This alliance of biomedical research and activist communities has served as a model for advocacy around other global issues such as breast cancer, tobacco control and access to essential medicines, including medications for non-communicable
Research in action: from AIDS to global health to impact

diseases. Fourth, the HIV pandemic secured enormous international funding (Global Fund, World Bank, PEPFAR) that is increasingly moving from ‘vertical’ (disease-specific) to ‘horizontal’ (general health system) approaches [25]. When Joep founded PharmAccess in 2000, his primary concern was to bring life-saving ARVs to people in Africa. Soon, he realized that true equity in health required a systems approach, after which PharmAccess pioneered an integrated demand and supply side approach to improving access to affordable and quality health care for all. Finally, HIV inspired increased international academic engagement and leadership, something that Merson described as ‘dear to Joep’s heart.’ Today, global health is a discipline in over 100 universities in the United States of America alone.

Just a few days before the symposium in Amsterdam, the extensive international media coverage on the recent Ebola outbreak often included CDC director Tom Frieden’s remark that: ‘In my 30 years in public health, the only thing that has been like this is AIDS. We have to work now so that this is not the world’s next AIDS.’

Merson reflected on the parallels between the early days of HIV and the Ebola virus outbreak, which include the stigma involved, the limited knowledge of the disease, the fact that it was originally presumed to be deadly in all cases, the lack of effective treatment and the inadequate global response. As such, he underscored the importance of learning from the consequences of the slow initial response to HIV. Ebola should also be considered a global security threat which requires a prompt and proactive response.


**From research to action**

*‘Programs finish, and whether they fail or succeed they are discontinued… there is scant attention paid to carefully embedding successful programs into sustainable national programs. And no one is outraged.’*

Prof Eric Goosby.

Prof Eric Goosby first met Joep in San Francisco in 1984, where Goosby was treating the first AIDS patients at San Francisco General Hospital. ‘Joep had a laser focus on the individual, on honouring the link between the physician and the patient. His authentic
way of living continues to reverberate with me and I am honoured to be a part of this collective acknowledgement of Joep’s contribution.’

Goosby’s presentation focused on global health delivery, diplomacy and the long road to sustainable health-care delivery systems. He addressed the challenge of equity in health and called for the prioritization of the principles of health-care quality, just as Joep had done. Goosby advocated that there are many diseases we know how to prevent, diagnose and treat effectively, yet efforts are falling short. ‘We know what works but we are not delivering. The fact that we are not doing so is impacting millions of lives and costing billions of dollars around the world. How can we encourage and promote development when tuberculosis and HIV are still ravaging the young and productive core of many African societies?’

According to Goosby, science has given us the tools, but most development efforts take an inordinate amount of time to implement. ‘We need to provide countries with external funding, without creating parallel systems of care. We cannot afford to be in a constant state of emergency when dealing with epidemics.’ Goosby referred to the Ebola outbreak as the canary in the cage to identify weaknesses in the medical delivery system and called for stronger partnerships. ‘Health systems need all four legs of the “delivery stool”: academia (rigor), the private sector (efficiency), the community (ownership) and the national and local government (management).’


How public policy can deliver health results

‘With PharmAccess and the Health Insurance Fund, Joep improved healthcare quality and created health insurance schemes that ensured that people are no longer a disease or a mosquito bite away from complete destitution.’

Ambassador John Simon.

Ambassador John Simon underscored his appreciation for Joep’s pragmatic approach. ‘We know what to do, yet it’s not getting done. Joep found this unacceptable. He knew that in order to achieve results, you need to influence public policy and to make a difference on the ground, not from behind your desk.’

In many developing countries, Ambassador Simon explained, the limited functioning of the state and its institutions hampers the development of health care and thus
universal access to quality health services. Most of these countries are ruled by a power elite that maintains a state that is designed to serve a limited elite as opposed to overall society. Building on the theoretical framework of Nobel Prize for Economics laureate Douglass North, Simon took the audience through the historic developments of governments moving from being extractive (limited access orders) to becoming inclusive institutions (open access orders).

He continued to describe the PharmAccess approach of simultaneous strengthening of demand and supply to turn the vicious cycle of malfunctioning health systems into a virtuous cycle. By combining interventions such as standards for quality improvement, loans for health-care providers, health insurance plans and mHealth, PharmAccess builds trust in the health-care system.

**The private sector and global health goals**

*Joep realized the importance and potential impact of market dynamics and how that can be catalytic in health.*

Fola Laoye.

‘Meeting Joep was a life-changing experience for us at Hygeia,’ said Ms Fola Laoye, chair of the Board of Hygeia, Nigeria’s largest health maintenance organization. She commended Joep’s continuous commitment to involve the private sector in health and health-care financing. Elaborating on what she called the African contradiction, Laoye explained that when it comes to health care, a good deal of spending comes from private pockets. ‘The private sector has a huge role to play in public health. While we are making progress, being here today and listening to everyone’s presentations makes me realize that our work is not done.’

Laoye shared several examples from the shared PharmAccess and Hygeia shop floor. Focusing on the Kwara State Health Insurance Program, set up in partnership with the Kwara State Government, she spoke of how this programme has improved the quality of health care at clinics and increased use of modern health-care providers, as well as improved health outcomes. ‘In areas like non-communicable diseases, malaria and maternal health, we have seen indices like we never expected.’

The programme, which was recently named as one of the finalists in the OECD DAC Prize for Taking Development Innovation to Scale, has had a significant impact on the rural populations of Kwara, one of the poorest states in Nigeria. In-depth impact evaluations conducted by the AIGHD have resulted in many publications, including a
paper in JAMA Internal Medicine [26] showing the positive effect of health insurance and facility quality improvement on blood pressure in adults with hypertension.


Panel discussion
Dr Khama Rogo shared with the audience that he saw Joep as a health revolutionary, referring to him as the Che Guevara of global health. ‘By nature,’ he said, ‘revolutionaries ask questions that are uncomfortable,’ and in this tradition Dr Rogo led the panel of eminent speakers in an animated discussion on global health and possible solutions to today’s biggest challenges. After stirring up the discussion with statements such as ‘Of all the ills that kill the poor, none is as lethal as bad government’, Rogo ended the session with the shared conclusion that we must all work to make sure that health is no longer a footnote in budget discussions and public policies. After all, as he proclaimed, ‘It’s not enough to be a doctor or a researcher, if you’re not also an activist.’

Closing remarks
PharmAccess Managing Director Onno Schellekens reflected on Joep’s conviction to drive results, whether the road to such results was politically convenient or not. ‘He started with mother-to-child transmission of HIV studies in 1995, at a time when no one wanted to finance such studies because finding a solution brought with it the responsibility of addressing the problem. He pushed through and insisted on doing the trials and developing treatment, even though the political buy-in was not yet there.’

When antiretroviral therapy became affordable and the regimens less complex, Joep founded PharmAccess to increase access to treatment for those who needed it most. To Joep, the fact that HIV/AIDS treatment was not available in Africa was – at best – a lack of will mixed with stupidity. At worst, it was pure racism. ‘Joep was always one step ahead,’ Schellekens said. ‘He taught us that doctors who can talk economics can change the world. While working to change policies at governmental level, Joep remained determined to deliver care all the way to the local last mile.’

Wrapping up the symposium, chairs Dr Zewdie and Prof Kazatchkine summarized the day as follows: From the first case of AIDS Joep Lange saw in 1983 and his first trip to the African continent in 1992 to the first treatment successes in 1996 in providing access to antiretroviral therapy in resource-poor settings, Joep advocated to treat all
HIV-affected persons equally. From the public sector to the private sector, from activists to pharmaceutical companies, from scientists to patients, Joep involved all parties.

Commemorating Joep’s awe-inspiring achievements towards universal access to HIV treatment, global health and universal health coverage, we continue to be inspired by him today. Let us be determined doctors, humanitarians, scientists, activists, economists, provocateurs and health revolutionaries who get things done in the field of HIV and global health. Let us continue Joep’s legacy.

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