

HIV: A DISCOVERY OPENING THE ROAD TO NOVEL SCIENTIFIC KNOWLEDGE AND GLOBAL HEALTH IMPROVEMENT

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by

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THE EARLY DAYS

The story begins more than twenty-five years ago, when the initial clinical observations of a alarming new epidemic were made. In June 1981 clinicians in the United States first reported a number of cases of *Pneumocystis carinii* in homosexual men¹. Subsequently the first cases of what would later be known as AIDS were observed in France. At the time, I was working at the Institut Pasteur with Luc Montagnier and Jean-Claude Chermann. In December 1982, we were contacted by clinicians in France who provided us with a lymph node biopsy from an AIDS patient, with the aim of isolating the etiological agent causing the disease.

The hypothesis at the time was that a retrovirus might be the etiological agent responsible for AIDS. The only human retrovirus known at that time was the Human T-lymphotropic virus (HTLV), known to cause transformation of T cells, and arguably it would have been possible to culture the cells from the lymph node biopsy, and simply observe for T cell transformation. Luckily we did not assume that HTLV was necessarily the cause of the disease, and we decided to sample the culture supernatant every three to four days to screen for reverse transcriptase activity. Indeed we started to observe reverse transcriptase activity, which decreased shortly after that, in correlation with cell death. Initially we were concerned about possible toxicity related to tissue culture components, but following the addition of fresh lymphocytes and fresh components to the culture, the same cell death phenomenon was observed in correlation with the detection of reverse transcriptase activity. We thus realised that the virus itself was responsible for this phenomenon.

The isolation of this new human retrovirus (at the time known as LAV, lymphadenopathy associated virus) was first reported and published in May 1983². In this first report we described that LAV could be propagated in peripheral blood mononuclear cells and in cord blood lymphocytes. We also described the viral protein p25, and importantly we determined that there was no, or weak, cross reactivity with HTLV-1 proteins, indicating that we

were dealing with a new human virus. In the same report we demonstrated the presence of antibodies against LAV in a second patient affected by AIDS. The report of the virus was, however, just the beginning.

The isolation of the virus was not sufficient to convince the scientific community of the implication of the virus in AIDS. It was therefore essential to further characterise the virus and establish a clear link between the virus and the disease to persuade the scientific community and the relevant authorities that the newly isolated virus was the etiological agent responsible for the emerging epidemic. In 1983 we decided to immediately halt all other research projects which were ongoing in the laboratory (including determining whether MMTV sequences could be associated with breast cancer – a hypothesis still valid today) and to mobilise a network of efficient collaborations with clinicians, immunologists and molecular biologists. In order to determine whether this newly isolated virus was truly responsible for the disease affecting AIDS patients, we quickly developed a serological test to perform sero-epidemiological studies³. Crucially, this same test was subsequently used as a diagnostic tool for blood testing. The development of the diagnostic test was made possible by a strong and efficient partnership with the private sector, namely Sanofi Pasteur.

In 1984 R. Gallo and colleagues and J. Levy and co-workers published reports confirming the identification of the causative agent of AIDS^{4, 5}.

FROM BED-SIDE TO BENCH TO BED-SIDE

These early years of HIV research were the reflection of clinical observations, which prompted basic research in the laboratory, which in turn resulted in the development of clinical tools. The identification and the initial characterisation of the virus led to the first diagnostic tests that permitted blood testing for the virus, and consequently the prevention of transmission by blood and blood derivatives. The increasing knowledge of the virus, its proven link to AIDS and its modes of transmission spurred the first programmes for voluntary counselling and testing and subsequently prevention of sexual transmission. The knowledge that the virus infected cells bearing the CD4 receptor⁶⁻⁸ and the fact that HIV could be cytopathogenic to CD4 lymphocytes was the basis for CD4 cell monitoring in HIV infected patients. The characterisation of viral reverse transcriptase activity provided the rationale for first using azidothymine (AZT) as therapy for HIV patients⁹ and, importantly, as the first therapeutic approach to prevent mother-to-child transmission of HIV. The efficiency of AZT alone was rapidly reported to be limited in regards to the first observation of resistance to monotherapy. These observations led to the development in the early 1990s of combined therapy, also known as highly active antiretroviral therapy (HAART). The cloning and sequencing of HIV^{10, 11}, performed by molecular biologists at the Institut Pasteur, provided the necessary knowledge of the basis of the test to determine the viral load and to monitor resistance to therapy (Figure 1).

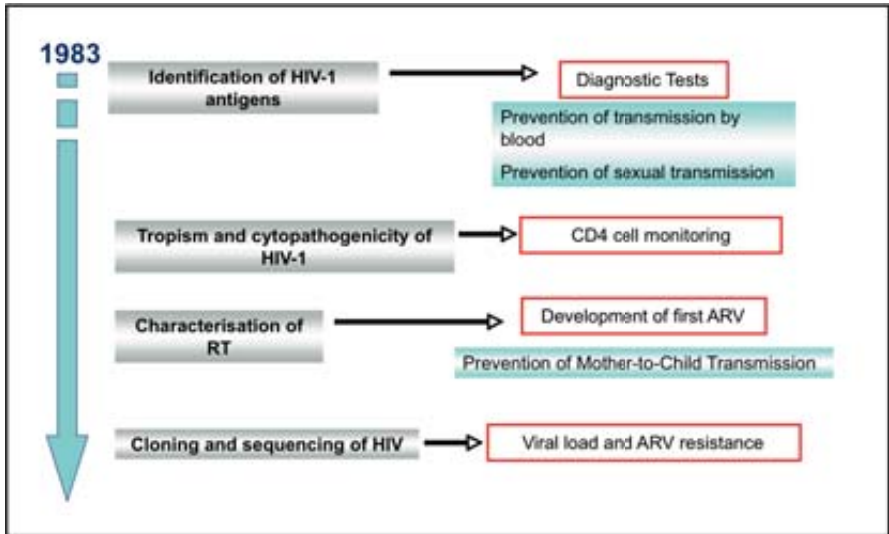


Figure 1. HIV research: from bed-side to bench and back to bed-side.

The cloning and sequencing of HIV also permitted researchers to gain insight into the tremendous diversity and the origin of HIV. Early studies indicated that HIV-1 may have resulted from the introduction of a virus from chimpanzee to humans. A collaboration with the Centre Pasteur Cameroun identified a new group of HIV-1, isolated from a woman with AIDS: the HIV-1 group N, distinct from groups O and M. Sequencing of simian viruses revealed a chimpanzee virus very closely related to the HIV-1 N group, in particular in specific genes^{12, 13}.

DETERMINANTS OF HIV PATHOGENESIS

Since the discovery of the virus, we have learnt that HIV infection is much more complex than we initially thought, and the mechanisms leading to AIDS pathogenesis are still today not entirely understood. We have, however, gained significant insight into the virus and the evolution of the disease it causes; for example we now know that soon after infection by HIV, the virus integrates into the host cells, establishing permanent reservoirs. Studies have shown that the evolution of the infection and the progression of the disease are linked to the viral load: indeed the peak of viral load correlates with a sharp decrease in the number of CD4 cells, which are partially restored in relation to the decrease of the viral load. In recent years, we have made important progress in understanding that HIV infection causes chronic immune activation. Very early after exposure to the virus, HIV infected patients are characterised by markers of generalised and persistent T cell activation. Given the close correlation between immune activation and the disease outcome, markers of T cell activation may emerge as better prognosis markers for disease progression than viral load and CD4 cell counts. It is also known

today that HIV infection results in early massive depletion of CCR5+ CD4+ T memory cells in the gastrointestinal tract, associated with microbial translocation in the gut. Further studies will be necessary to determine whether the microbial translocation is a cause or consequence of massive T cell depletion^{14, 15}.

The evolution and progression of the disease caused by HIV is closely linked to a number of determinants of both the virus itself and the host. Indeed each particular path of disease progression is determined by a delicate interplay between viral and host factors. The virus itself greatly varies: in its tropism and replicative capacity, as well as the intrinsic immunosuppressive properties of some viral proteins, all influencing HIV pathogenesis. A number of host factors are also important in determining the distinct paths of disease progression in different HIV infected individuals. The adaptive immune responses (including CD8 cell and CD4 cell responses) are finely tuned in each separate individual, resulting in differential control of the infection. Equally different genetic polymorphisms of receptors, ligands and key immune proteins all result in specific modulations of the host response to HIV infection. Recently it has become apparent that humans and non-human primates possess a number of proteins capable of restricting HIV/SIV infection, and therefore play crucial roles in intracellular innate immunity. In brief, therefore, the specific evolution of the disease caused by HIV is the result of an intricate interplay between the virus and the host.

NATURAL MODELS OF HIV/AIDS PROTECTION

Natural models provide key insight into the mechanisms which underlie protection against HIV infection and disease progression.

A very small number of individuals (known as exposed uninfected, EU) appear to be resistant to infection, despite repeated exposure to HIV. A study, performed in collaboration with Vietnam, analysed two groups of intravenous drug users (IDU) who routinely exchanged needles for drug injection. Despite both groups being infected with hepatitis viruses and HTLV, one group was consistently negative for HIV in both serological and PCR tests. To address the mechanisms involved in this natural protection against infection by HIV, the innate immune responses of the two groups were compared. The two groups were characterised by a significant difference in the activity of the natural killer (NK) cells; in fact the EU group of Vietnamese IDU typically showed an increased level of NK cell activity¹⁶. We further analysed the NK cell repertoire associated with this increased activity. The analysis revealed an increased ratio of specific NK receptors in EU compared to control or HIV infected individuals. Furthermore, the functional activated NK cells in EU express significantly higher levels of the CD161 receptor than control individuals, suggesting that a specific subset of NK cells in EU might be involved in their protection against HIV infection.

Another insightful model, which permits us to shed light on some of the mechanisms providing protection against HIV, is provided by the few indi-

viduals who, despite being infected by the virus, are capable of controlling its replication. These rare individuals (known as HIV controllers, or elite controllers) are defined by having been infected for more than 10 years while presenting undetectable plasma viral RNA, despite being naïve of antiretroviral therapy. In 2007 we reported that the CD8 T lymphocytes of HIV controllers possess HIV suppressive capacities, being able to suppress HIV replication in the CD4 T cells^{17, 18}. The majority of HIV controllers included in this first study possess CD8 T cells capable of eliminating infected CD4 T cells. Further analyses showed that the CD8 T cells of HIV controllers were activated, but to a lesser extent than in HIV progressors. Although the majority of HIV controllers appear to possess suppressive CD8 T cells, some individuals are not characterised by this trait, while still efficiently controlling the virus. This observation indicates that there is likely more than one immune mechanism contributing to the tight control of HIV replication in these lucky few individuals.

Animal models represent a key component of many domains of biomedical research. HIV and its closely related counterpart, the Simian Immunodeficiency Virus (SIV), are strictly primate-specific viruses, so simian models which are susceptible to SIV infection play a key role in understanding infection and disease progression. Most naturally infected African primates, like the African Green Monkey (AGM) do not develop AIDS, in contrary to the Asian Rhesus Macaque; they therefore provide a unique model to investigate protective mechanisms against AIDS^{19, 20}. Interestingly, SIV is capable of replicating in both pathogenic and non-pathogenic simian models, suggesting that viral replication is not the only key determinant of an AIDS outcome. Both models show a massive depletion of CCR5⁺ CD4⁺ cells in the gastrointestinal tract. Partial restoration of CD4⁺ cells and the absence of apoptosis, however, ensure that the intestinal mucosa remains intact in the non-pathogenic model, therefore impeding microbial translocation. Comparative analyses between the two primate models show that T cell activation during the chronic phase of viral infection is a key difference between the non-pathogenic and the pathogenic infections. Indeed chronic T cell activation is the hallmark of HIV-1 infection in humans and pathogenic SIV infection in Rhesus Macaques. The profiles of T cell activation are determined by the innate immune responses, mediated in particular by dendritic cells. The Rhesus Macaque model shows a more persistent recruitment of plasmacytoid dendritic cells (PDC, the principal producers of interferon- α) to the lymph nodes^{21, 22}. More recently we have used microarrays to compare the gene profiles of the two primate models. This technique has allowed us to observe that interferon type 1 pathways are activated in both models, but only transiently in the non-pathogenic model in the very early phases of infection. This observation contributes to the hypothesis that key events which determine the disease progression occur in the very early stages of infection. Important differences are observed in the early acute phase of SIV infection in the non-pathogenic and pathogenic models, including a higher induction of pro-inflammatory cytokines in the pathogenic model (Figure 2).

		SIVagm	SIVmac
		Non-pathogenic	Pathogenic
marker			
T cell activation		+	+
Intestinal Mucosa	CCR5+CD4+ depletion	+++	+++
	Microbial translocation	-	+
Cytokines	TNF- α , IL-6, IL-12,	-	++
	TGF- β 1	+	+
	Smad7	-	+
Recruitment of PDC to LN		+	++

Figure 2. Non-pathogenic versus pathogenic SIV infection – early acute phase markers.

The early acute phase of HIV infection appears, therefore, to be crucial in determining disease progression. Given the importance of this very early phase following infection, the role of the innate immune system, our body's first line of defence against infections, should strongly be considered.

More detailed insight into the role of the innate immune system in HIV has been gained by an *in vitro* model of a co-culture of natural killer (NK) cells and dendritic cells (DC), which are natural target cells of HIV infection. This *in vitro* model has highlighted that the expression of a number of NK cell surface receptors, in particular the CD85j receptor, is reduced when the cells are in contact with infected DCs. We also observed that the subpopulation of NK cells which express the CD85j receptor is capable of strongly suppressing HIV replication in DCs²³. This suppression is only partially relieved by incubation with monoclonal antibodies against HLA class I (the natural ligands of CD85j) but strongly abolished by incubation with a recombinant CD85j protein, suggesting that the interaction between the CD85j receptor and a peculiar (as of yet unknown) ligand might result in signalling pathways necessary for suppression.

Future research will need to focus on understanding in greater detail the complex cross-talk between DC, NK and T cells during HIV infection, as well as the modulation of signalling pathways and soluble factors which can influence disease progression (Figure 3).

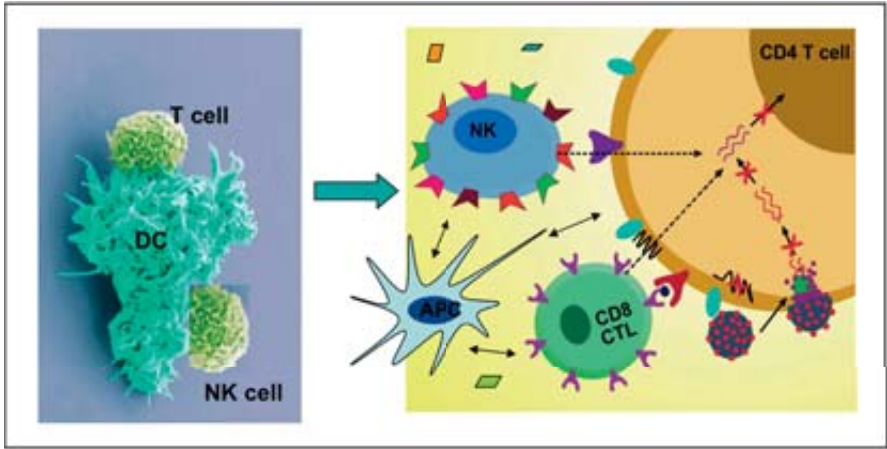


Figure 3. Potential mechanisms of HIV control. The control of HIV may be determined by a complex interplay between innate and adaptive immune systems. Natural killer (NK) cells might control HIV by directly eliminating infected cells or by providing the optimal cytokine environment. HIV-specific CD8 cells with cytotoxic properties could also play a key role in controlling HIV infection. Other control mechanisms include the production of neutralising antibodies and intracellular restriction factors which counteract the HIV replicative cycle.

HIV/AIDS: THE STATE OF THE EPIDEMIC IN 2008 AND FUTURE DIRECTIONS

At the end of 2007, 33 million people were living with HIV, 2.7 million were newly infected and a further 2 million died of AIDS²⁴. These numbers demonstrate that HIV/AIDS still remains a crucial global health issue. Since the discovery of HIV, enormous progress has been made in the development of antiretroviral (ARV) drugs, and in expanding their availability to those who require treatment. In 2002, only approximately 2% of people needing treatment received it; this figure has since increased to 30% in 2008. Despite this massive increase in access, for every new person starting ARV treatment, 2–3 new cases of HIV infection are reported. The benefits of ARV are irrefutable; their importance is clearly illustrated in Botswana where the introduction of ARV in 2002 has been followed by a decrease in the number of AIDS-related deaths in the country.

Despite the immense benefits of ARV treatment, many issues still need to be tackled. ARV treatment remains a life-long commitment with consequent economic limits. Moreover, life-long treatment is associated with the emergence of drug resistance, metabolic disorders and cancers. In the absence of a cure for HIV, it is essential to continue investigating and promoting all prevention measures. The accomplishments of prevention programmes for HIV infection have been proven by the success in limiting sexual transmission (mainly through the promotion of condom use) and in limiting mother-to-child transmission of HIV by improving diagnosis and introducing ARV treatment to pregnant HIV⁺ women. Research on prevention methods continues,

and recently we have also learnt that male circumcision can diminish the risk of infection, and therefore could be considered as part of a comprehensive prevention plan. Prevention programmes which are currently being investigated include pre- and post-exposure prophylaxis, and further research directed on specific anti-viral microbicides, which so far have only provided disappointing results, could lead to beneficial outcomes.

Despite innumerable advances in the field of HIV research over the last twenty-five years, many new aspects of HIV infection and immunopathogenesis are still emerging. It is clear that there are currently many areas of HIV research which require investigation, and many domains will benefit from a strong emphasis on basic research. Further insight into the very early stages of HIV infection, including the establishment of viral reservoirs and the immune responses induced, is crucial for the development of novel therapeutic and vaccinal strategies. Future directions for new intervention strategies which should be investigated in further detail include, for example, the identification of new targets and the use of siRNA to restrict HIV infection. Recent years have highlighted the central role of chronic immune activation in disease progression; if microbial translocation is confirmed to be responsible, at least in part, for this immune activation, drugs limiting microbial translocation need to be considered as alternative therapeutic strategies.

Co-infection between HIV and other diseases should not be overlooked. Co-infections in HIV⁺ patients are currently an acute public health issue, and further clinical attention and basic research are required to address this delicate problem. A salient example is provided by the co-infection of HIV and tuberculosis: in sub-Saharan Africa and other resource-limited regions, tuberculosis is a major cause of death among people living with HIV.

An effective vaccine against HIV represents the ultimate prevention approach. HIV, however, exhibits several scientific challenges. HIV is a virus characterised by a high degree of genetic variability, enabling the virus to evade the human immune system. Furthermore, the very early establishment of viral reservoirs, characteristic of HIV, hinders the development of an effective vaccine. To add to the complexity, HIV is transmitted not only by cell-free virus, but also by cell-to-cell contact, and it is still unclear what mechanisms are necessary to impede cell-to-cell transmission. To achieve progress in the development of an effective vaccine, it is essential to understand the complex dysfunctions of the immune system which are more rapidly induced by HIV than the specific immune response following infection. A key step in the development of an effective vaccine will be the identification and definition of the viral determinants responsible for early pathogenic signals and mechanisms to prevent such harmful pathogenic pathways²⁵⁻²⁷ (Figure 4). In addition to the indispensable advances in basic science, the development of an effective HIV vaccine requires innovative and creative strategies, within the context of a clearly defined international agenda to promote collaboration.

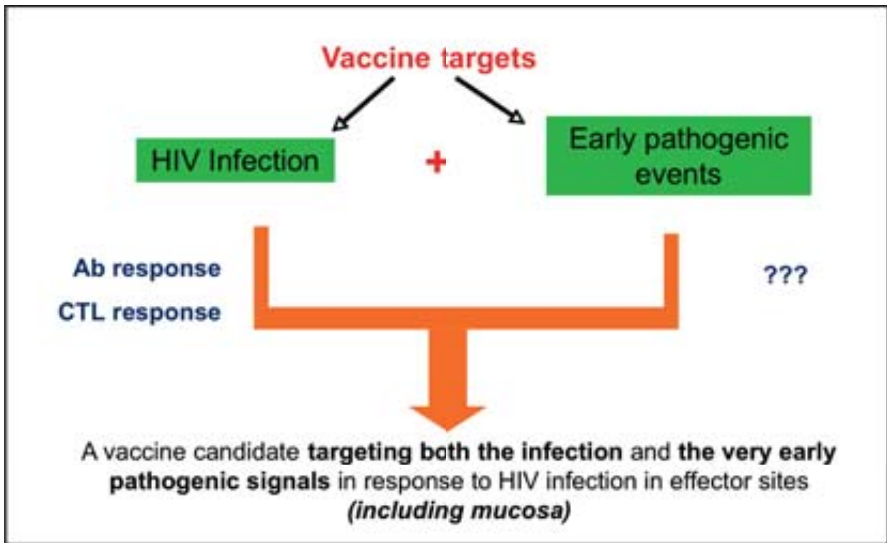


Figure 4. HIV vaccine research: re-thinking future strategies.

BENEFITS BEYOND HIV/AIDS

HIV can be a powerful tool for unravelling future scientific knowledge. Research on HIV has significantly contributed to the understanding of the delicate relationship between viruses and hosts. Continued effort to understand this complex virus has also revealed novel cellular partners which may be involved in controlling infection. HIV can also help identify new receptors and ligands and novel signalling pathways. Future research on understanding the immune responses induced by HIV will provide more information on the complex cross-talk between innate and adaptive immunity. This cross-talk between innate and adaptive immunity is crucial for the induction of effective immune responses to infections, and the elucidation of these mechanisms will prove important for other diseases as well.

Given the complexity of developing an effective HIV vaccine, we need to think of new innovative and creative concepts and strategies for vaccines. These new strategies may likely prove useful for the development of vaccines against other infectious diseases or even cancer.

The use of lentiviral vectors in gene therapy for a number of diseases, including cystic fibrosis and muscular dystrophy, has already been widely investigated. Despite some setbacks, new promising results are encouraging. The field is still at an early stage, but further research may provide new therapeutic strategies.

IMPROVING GLOBAL HEALTH: A KEY ROLE OF THE FIGHT AGAINST HIV/AIDS

Importantly, the fight against HIV is also a key element in the improvement of global health. It is now widely recognised that investment in health is one of the key components of sustainable development. International efforts in close collaboration with national programmes in HIV/AIDS have promoted an overall amelioration of global health, which is not limited to people living with HIV. Global interventions in HIV/AIDS reinforce local infrastructure, contribute to capacity building and increase human resources, contributing greatly to better overall health in a country (Figure 5).



Figure 5. Benefits beyond HIV: global health systems improvement.

The effect of HIV/AIDS interventions on general public health improvement is exemplified by the case of Cambodia. In 1994–95, we started working in collaboration with Cambodia. At the time, human resources were extremely limited, if at all existent. We and others quickly started to train people, who were very keen and determined to learn about progress in science and medicine. In 1995, the first Voluntary and Confidential Counselling and Testing (VCCT) site was created at the Institut Pasteur in Cambodia. Over the years, we and others have been working to improve the quality of human resources in the country, the quality of health infrastructures and the number of VCCT sites has greatly increased to more than 200 in the entire country in 2008. A similar trend was noted in clinical sites for treatment of opportunistic infections and antiretroviral therapy. These sites are present in the entire country, covering a large part of its territory, and the services provided are not only HIV monitoring and treatment but also care for other infections. Today,

approximately thirty thousand patients are under antiretroviral therapy and Cambodia may well be one of the first countries to reach the objective of universal access by the year 2010. Such progress would not have been possible without the strong political determination of the government.

Although the road ahead is still long, we are on the right path to achieve a world without AIDS. This goal will be reached by following a model of research, echoing the tradition of Louis Pasteur: continued basic and clinical research, investment of both public and private sectors, public health interventions and the participation, which should be strongly acknowledged, of people living with HIV/AIDS.

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Portrait photo of Françoise Barré-Sinoussi by photographer Ulla Montan.