HIV infection and AIDS: new information, new hopes

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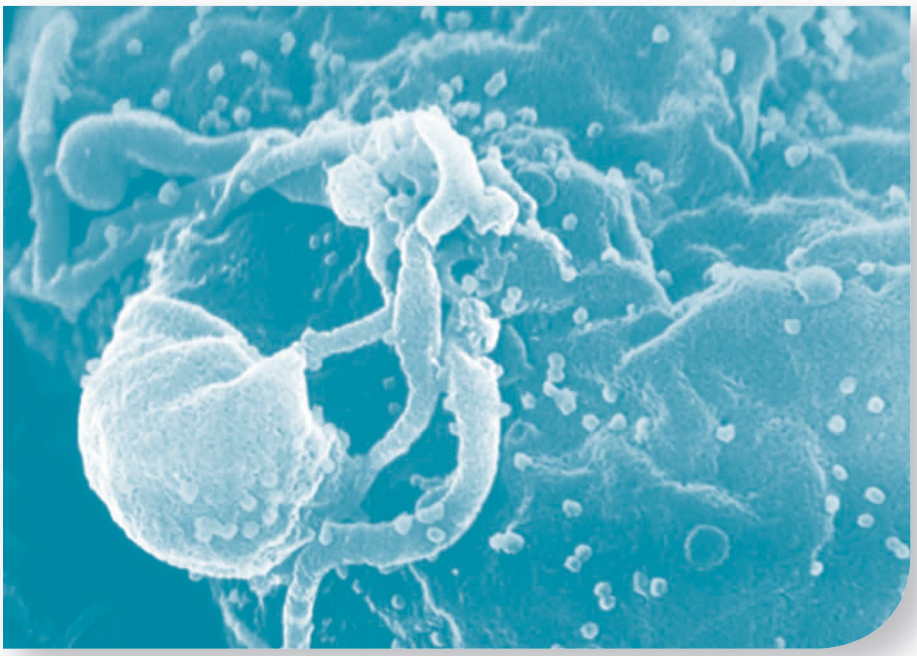
Introduction

At the IFR 113 "Immunity-Cancer-Infection" research institute at Pierre-et-Marie-Curie University, the "Immunity and antiviral and vaccine Immunogenetics" team led by Prof. Brigitte Autran, conducts research on HIV immunity and the related immunopathology. The group is working to develop and assess new immune interventions for the long-term control of the infection, the reduction of viral reservoirs, and even the eradication of the infection. The group's translational research and the links developed between fundamental and clinical research have earned it international recognition in the field. Since 2011, SCOR Global Life has been privileged to have signed a partnership agreement with Pierre-et-Marie-Curie University.



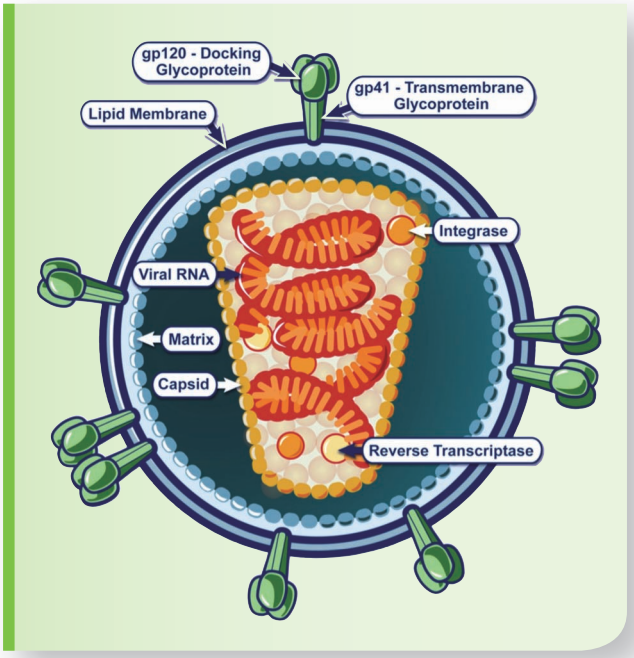
So, what is the latest information on AIDS and human immunodeficiency virus (HIV) 30 years after its discovery and 15 years after the introduction of powerful treatments which have changed the course of the disease in the countries where these drugs are readily available? The HIV/AIDS pandemic is still one of the greatest medical threats at the beginning of the 21st century, with over 35 million people infected in 2010. Do the research results give us cause for hope? Is the revolution in AIDS therapies continuing at a time when the pandemic is clearly persisting and there is no vaccine within sight?

This publication reports on the main advances which have radically changed our understanding of the disease caused by this virus in the last few years. Therapeutic strategies have been improved and their benefits and possible complications have become clearer opening the perspective, still some way off it is true, but nevertheless more and more credible, of a cure and even the eradication of this infection.

The treatment revolution continues

Fifteen years after the introduction of combination antiretroviral therapies, otherwise known as tritherapies, the long-term success of this strategy is undeniable [1].

Structure of the HIV (NIH)



The very extensive COHERE study of HIV Infection in 80,642 Europeans with an average age of 37 years, treated for a median period of 3.5 years and with a nadir CD4 cell count of 225/mm^3, recently showed a mortality rate of 1.2/100 person-years, 4.2 times higher than the general population [2].

However, this rate fell to 0.37/100 person-years, similar to that of the general population, among the 35,316 individuals who had satisfactorily restored their immunity with CD4 T-cell counts of 550/mm^3, particularly in men who were non-drug abusers and women after 3 years. This study concluded, in line with the results of other French or international cohorts, that **mortality rates for most people infected with HIV who are not intravenous drug abusers and who are under treatment were comparable to those of the general population.**

New concepts in HIV infection

The discovery of AIDS and the HIV virus revealed very early on that this virus infects certain white blood cells responsible for the immune defences, penetrating them and binding onto receptors, particularly the CD4 receptors. The infection is permanent and transfers from cell to cell, causing the irremediable loss of cellular immunity and resulting in AIDS.

Research carried out over the last few years has enabled scientists to refine these concepts and get a better understanding of the obstacles to developing a vaccine and curing this infection. In addition, it has enabled the identification of new conditions caused by HIV infection.

Immediate and permanent infection of all the immune tissues occurs within just a few hours of contracting the HIV

The virus was discovered in white blood cells taken from patients' lymph nodes by the team at the Pasteur Institute in 1983, before the American teams who were looking for it in the blood cells, and earned them the Nobel Prize. However, for a long time this particular point was seen as a detail and it is only in the last 5 to 8 years that its true importance has become clear.

We now know that the virus infects the lymph nodes within a few hours of entering the body and that it spreads in less than a week into the entire immune defence system, or lymphoid tissue, from where it can no longer be dislodged.

This is information of vital importance as it tells us that any attempt to prevent the disease, whether by means of a vaccine or a treatment, must be able to act immediately and whenever a person is accidentally exposed to the virus.

Immune activation, inflammation and comorbidities

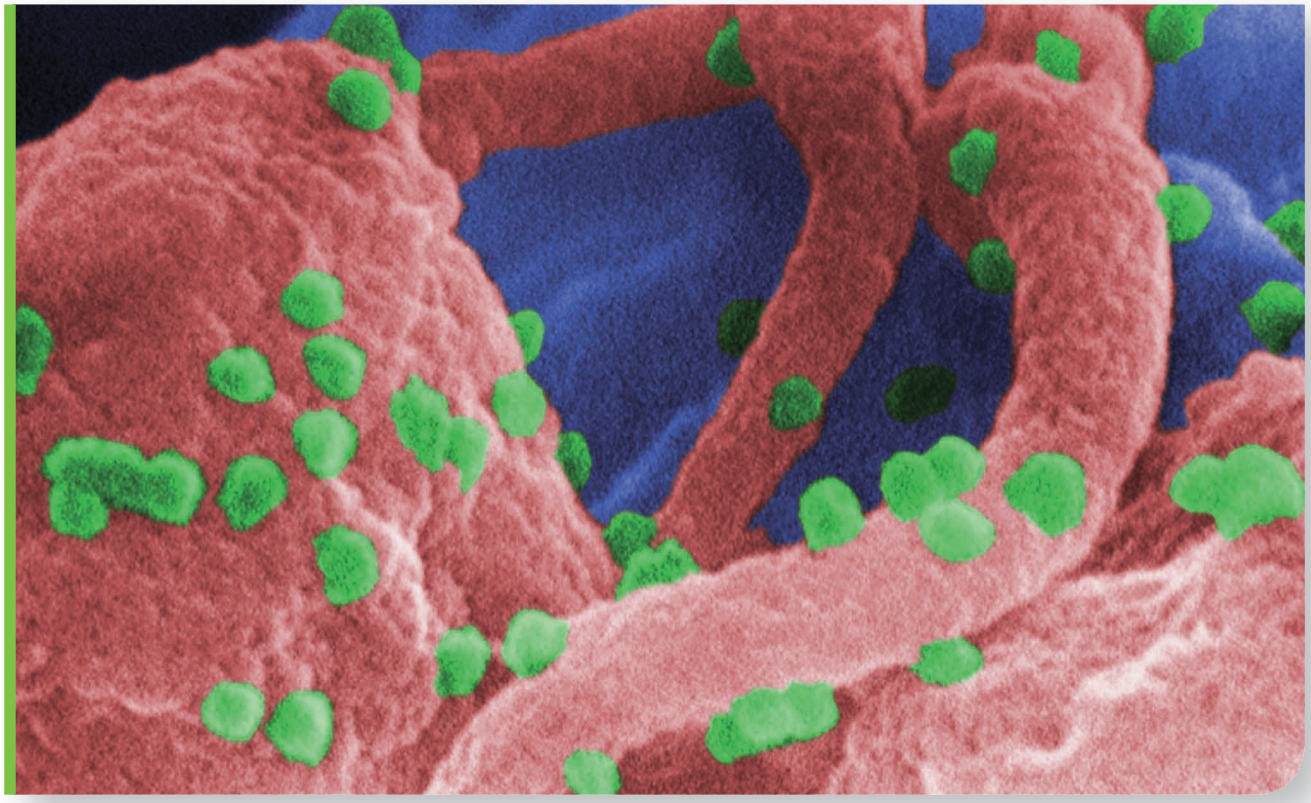
The discovery of AIDS followed by that of the HIV in the 80s led to the finding that the death of AIDS patients was directly linked to a deficiency in the body's immune defences (causing the immune deficiency syndrome) caused by the HIV infection. The extreme gravity of this deficiency and the constant mortality within ten years meant it was impossible to analyse the other deleterious consequences of HIV infection on the body.

The victories won in the treatment of HIV, which have removed the spectre of AIDS in treated patients, have brought to light these other effects, or comorbidities, long thought to be side effects of the treatments, but in fact directly linked to the virus.

This chronic infection of the immune system, before causing AIDS, actually induces a chronic general inflammation whose consequences lead to accelerated ageing of the immune system, but also to cardiovascular, bone and neurological complications as well as contributing to the emergence of cancers, independently of the immune deficiency.

How does the virus cause this chronic inflammation? The immune system reacts to the invasion of HIV, as it reacts to that of any virus, by activating the subject's immune defences. Furthermore, the white blood cells directly targeted by the virus, the CD4+ T cells and the macrophages produce a large number of soluble factors, so-called pro-inflammatory cytokines and chemokines, which activate all the body's tissues to create an activation state, the permanent nature of the infection being responsible for the persistence of the chronic inflammation.

HIV on the surface of a lymphocyte (CDC)



Comorbidities in patients with HIV

• Cardiovascular risk: The "SMART" years

The first major comorbidity unmasked by antiretroviral (ARV) therapies was the increased cardiovascular risk initially interpreted as a complication or direct toxic effect of the treatments. Several studies were set up at the beginning of the 2000s to attempt to assess the potential benefit of alternative treatments with the aim of reducing the quantities of these drugs and therefore their supposed toxicity. The most important of these studies, the "SMART" trial [3] had to be halted early by the monitoring board, which observed that the frequency of cardiovascular complications was in fact higher in the patients interrupting their treatment than in those in the continuous therapy arm.

Many other studies later confirmed these unexpected results, convincing the medical community that, although certain anti-HIV drugs could have side effects, it was the HIV infection itself, more than the treatments, which was directly responsible for this increased risk of cardiovascular disease. This increased risk, including complications as serious as myocardial infarction, varied from study to study, but was 2 or 3 times greater, especially in the 55 to 75 year age group.

The classic risk factors for cardiovascular disease are of course also present in these subjects, in particular tobacco dependency. Nevertheless, HIV infection directly causes chronic inflammation, which is objectively proven by the elevation of certain markers in the blood related to multiple vessel wall dysfunctions (the endothelial function), and also affecting the cells regulating lipids, with a reduction of total cholesterol and in particular a drop in "good" cholesterol, HDL, and causing an abnormal activation of coagulation factors.

As well as the increased cardiovascular risk, it also became clear that HIV-related chronic inflammation aggravates osteoporosis and the risk of pathological bone fractures. Above all, it was discovered that all these changes were more common and more serious the longer the period of infection before the introduction of antiretroviral drugs. The precise date of the HIV contamination being known, the length of this period of infection can be estimated by the lowest value of the blood CD4 T-cell count (CD4 T-cells being the white blood cells targeted by HIV) observed before beginning an antiviral treatment. This value defines the **"CD4 nadir"**, a marker which has today become essential in assessing the course of the infection and the possible increased risks connected to it. Furthermore, several of these anomalies are partially reversed by taking ARVs.

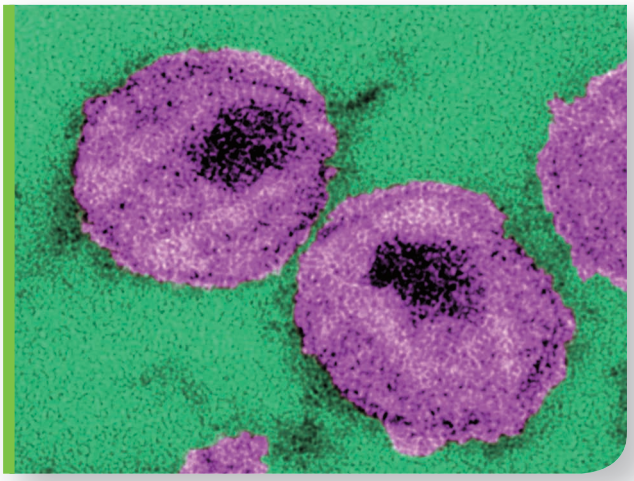
• Increased risk of cancer

These comorbidities are also marked by an increased risk of cancer, occurring independently of AIDS and at higher CD4 T-cell counts. Many international epidemiological studies have shown that although of course cancers directly linked to AIDS, lymphoma and Kaposi's sarcoma in particular, occurred between 20 and 1,000 times more often in subjects infected with HIV than in the general population, the frequency of cancers not related to AIDS also increased by a factor of 2 or 3 depending on the studies.

The ONCO-VIH national prospective study carried out by teams at Pierre-et-Marie-Curie University and La Pitié-Salpêtrière hospital with the ANRS and the Cancéropole Ile de France, showed that the incidence of cancers in infected patients was 14 per 1,000 person-years with an estimated relative risk of 3.5 (95% CI 3.3-3.8) and 3.6 (95% CI 3.2-4.0) in men and women respectively, and that it was particularly high in young subjects compared with the general population. The most common cancers were still non-Hodgkins lymphoma (21.5%) and Kaposi's sarcoma (16%), but they were followed by lung cancer (9.4%), anal cancer (8.2%), Hodgkin's lymphoma (7.6%), skin cancer (6.8%) and liver cancer (5.6%) [4]. Similar studies carried out on other cohorts in other countries found approximately the same rates.

By the end of the 2000s it was becoming clear that the benefits of early and prolonged antiretroviral therapies (ARTs) were much greater than their potential side effects. And so, while various national recommendations on antiretroviral treatment only required that the infection be treated where there was a risk of AIDS objectively proven by

HIV seen by electron microscope (CDC)



a CD4 T-cell count lower than 250/mm^3, the threshold for the introduction of these treatments was gradually raised to 350 then to 500/mm^3, where it stands now.

Spontaneous control of HIV infection and host genetics

In a few, very rare patients, known as long-term nonprogressors or elite controllers, the HIV infection remains stable for many years without any treatment and without progressing to AIDS. Many studies in several international cohorts, including the French cohorts studied by our team, based on the classic so-called candidate gene approach, have revealed a very high frequency of certain HLA groups (sorts of blood group with antigens expressed on the white blood cells and determining these individuals' immune defences) associated with this protection.

New approaches using "DNA chips" to analyse the entire genetic code have confirmed that the HLA system is in fact the strongest genetic marker and predominant factor in this control of the infection [5]. It is this special association with certain HLA groups that underlies the extremely powerful immune control classically observed in these subjects, a cell-mediated immunity combining auxiliary CD4 T-cell and CD8 cell non-cytotoxic anti-HIV responses. This cell-mediated immune control has been used as the model for the development of vaccines against the virus.

Prevention strategies and HIV vaccines: disappointments and hopes

The repeated failures of conventional approaches to vaccine development based on the induction of neutralising antibodies during the 1990s led researchers to consider new design strategies for candidate vaccines capable of inducing anti-HIV T-cells by a mechanism similar to the protection observed in nonprogressor subjects.

These new approaches mainly used recombinant viral vectors for the HIV genes and have shown good tolerance and quite good immunogenicity in phase I and II trials. Some very large studies have therefore been conducted with the two vaccines with the best efficacy. However, the STEP trial using a recombinant adeno-associated virus vector had to be halted prematurely due to an increased frequency in HIV infections in the vaccinated subjects compared to the subjects receiving the placebo.

Conversely, an even larger trial involving 16,000 Thai volunteers using another recombinant vector of the poxvirus-type associated with a viral envelope protein (trial RV144) achieved a statistically significant degree of protection in the vaccinated subjects compared with the control group. This first success reported in 2009 nonetheless remains insufficient, with a low rate of protection, of the order of 31%.

However, this trial did serve to demonstrate the key role played in this protection by anti-HIV antibodies induced by the vaccine. This has led to a revision of the new approaches developed since, now seeking mainly to induce antibodies, as in classic vaccine strategies. However, in spite of considerable efforts, no vaccine has yet been developed [6].

Concurrently, other approaches to prevention have been developed. The most remarkable are those that demonstrate the protective effect of circumcision, such as the ANRS 1465 study showing a level of protection between 40 and 50% [7], and especially the HPTN 052 study demonstrating the protective effect of early and universal antiretroviral therapy, which provides 90% prevention against the transmission of the infection [8]. These two approaches therefore provide considerably greater protection than that observed so far with the best of the HIV candidate vaccines.

The antiretroviral therapy revolution continues; the new challenge of eradication or remission

The success of ARVs

Antiretroviral therapies have radically improved outcomes for patients infected with HIV by controlling the virus by blocking the deterioration of the immune system and the disease and thereby massively reducing mortality and the comorbidities associated with the infection. This revolution is ongoing, with the development of molecules that are ever more effective, better tolerated and much simpler to administer.

As a result, in France and in several other countries, 90% of patients under ART have a virus that is undetectable in the blood. Furthermore, ART reduces the risk of transmitting the virus by 90%. This has led the International AIDS Society and the North American health authorities to recommend that ART be given to all patients infected with HIV whatever their CD4 T-cell count.

Finally, recent work by our team in particular has shown that maintaining these effective therapies for over 10 years allowed a continued improvement in the performance of the immune system, moving towards virtual normalisation [1]. However, numerous constraints remain. In particular, although these treatments effectively control the virus, they cannot eliminate it from the body, where it persists without multiplying, silently integrated in the chromosomes of resting cells, and referred to as reservoirs.

In fact, viral replication inevitably restarts from these reservoir cells if the therapy is stopped. Improper use of ARV drugs therefore exposes the subject to a risk of selecting viruses resistant to the drugs. This means that the treatment must be taken continually, for life. Although these drugs are now considerably less toxic, they remain very expensive (approximately 1,000 Euros a month), which weighs heavily on healthcare economies all over the world. As a result, today these therapies are accessible only to about 40% of the patients who need them, which unfortunately explains why the pandemic is still being perpetuated.

Cure or remission? Myth or true hope?

HIV infection remains a unique case in the history of infectious diseases as, 30 years after its emergence; it is still causing a deadly and insufficiently treated pandemic. Not a single case of the spontaneous disappearance of the virus has been reported so far and the treatments only control the virus without eliminating it.

However, a probable cure was obtained in one infected patient, who was unfortunately also suffering from acute leukaemia which required aggressive chemotherapy and a bone marrow transplant. This was taken from a donor who carried a mutation in one of the virus receptors. This gave the patient receiving the bone marrow a resistance to the virus which enabled him not to recontaminate the transplanted cells and to stop his ART completely.

Five years later, the HIV remains undetectable in this patient! Even though this is an absolutely unique case (known as the "Berlin patient") [9], this very first cure or remission is fundamental as it demonstrates that the concept of a cure is feasible. It has therefore generated real new hope and provided a new boost for research into therapies.

Research is therefore now turning to the theme of eradication or rather the remission of the infection. Eradication of HIV from a chronically infected individual still seems well out of reach insofar as the transplant strategy used in the case of the famous Berlin patient is far from applicable on a large scale and, in itself, causes complications.

Remission, in a similar way to the long-term remission obtained in cancer patients, refers to a persistent infection with no associated illnesses, where the virus persists at a very low level of replication, without any ART. Examples of remission recently obtained in 15 French patients lend credence to this concept.

They are the "post-treatment controllers" (PTCs) of the VISCONTI study. These patients have the particularity of having been treated very soon after their contamination without being carriers of any of the genetic traits mentioned above. When their ART was stopped after several years, there was no recurrence of viral replication for about 5 years. Intensive studies are now under way to try and understand the reasons for this success.

Prof. F Barré-Sinoussi, winner of the Nobel Prize for Medicine for the discovery of HIV, has launched, with the IAS, a major international research effort (Towards HIV Cure) [10] to develop new therapeutic strategies with the aim of extending these still exceptional observations. If the prospects of success are still some way off, there is no doubt that this new international boost for research will lead to new knowledge and new progress in overcoming HIV and AIDS.

Since the introduction of tritherapies, the survival of patients infected with HIV has improved considerably. This has only been possible thanks to access to medical care and drugs.

Since 2002 SCOR Global Life has treated this infection as an ordinary impaired risk, which is analysed and underwritten in the same way as other chronic conditions.

Advances in HIV/AIDS therapy, which have led to improved survival, are monitored closely by our teams in order to offer up-to-date selection and rating guidelines.

Currently, people under treatment, without any comorbidities, with an undetectable viral load and a CD4 T-cell count over 350 can be insured in the same way as other patients suffering from chronic conditions for a period of 20 years.

Recently, the insurability of HIV-positive patients was the subject of an article published by epidemiologists in AIDS [11].

We are following their lead on this subject and are updating our rating guidelines in order to keep pace with the improvement in prognosis and survival.

References :

1. Guihot A, Bourgarit A, Carcelain G, Autran B.Immune reconstitution after a decade of combined antiretroviral therapies for human immunodeficiency virus. Trends Immunol. 2011 Mar;32(3):131-7. doi: 10.1016/j.it.2010.12.002.

2. The Collaboration of Observational HIV Epidemiological Research Europe (COHERE) in EuroCoord: Lewden C, Bouteloup V, De Wit S, Sabin C, Mocroft A, Wasmuth JC, van Sighem A, Kirk O, Obel N, Panos G, Ghosn J, Dabis F, Mary Krause M, Leport C, Perez-Hoyos S, Sobrino-Vegas P, Stephan C, Castagna A, Antinori A, d'Arminio Monforte A, Torti C, Mussini C, Isern V, Calmy A, Teira R, Egger M, Grarup J and Chêne G All-cause mortality in treated HIV-infected adults with CD4 5500/mm3 compared with the general population: evidence from a large European observational cohort collaboration International Journal of Epidemiology 2012;41:433–445.

3. Strategies for Management of Antiretroviral Therapy (SMART) Study Group, El-Sadr WM, Lundgren J, Neaton JD, Gordin F, Abrams D, et al. CD4+ count-guided interruption of antiretroviral treatment. N Engl J Med. 2006 Nov 30;355(22):2283-96.

4. The spectrum of malignancies in HIV-infected patients in 2006 in France: the ONCOVIH study.Lanoy E, Spano JP, Bonnet F, Guiguet M, Boué F, Cadranel J, Carcelain G, Couderc LJ, Frange P, Girard PM, Oksenhendler E, Poizot-Martin I, Semaille C, Agut H, Katlama C, Costagliola D; ONCOVIH study group. Int J Cancer. 2011 Juillet 15;129(2):467-75. doi: 10.1002/ijc.25903. Epub 2011 Avr 27.

5. Dalmasso C, Carpentier W, Meyer L, Rouzioux C, Goujard C, Chaix ML, et al. .Distinct genetic loci control plasma HIV-RNA and cellular HIV-DNA levels in HIV-1 infection: the ANRS Genome Wide Association 01 study. PLoS One. 2008;3(12):e3907. doi: 10.1371/journal.pone.0003907. Epub 2008 Déc 24.

6. Burton DR, Ahmed R, Barouch DH, Butera ST, Crotty S, Godzik A, Kaufmann DE, McElrath MJ, Nussenzweig MC, Pulendran B, Scanlan CN, Schief WR, Silvestri G, Streeck H, Walker BD, Walker LM, Ward AB, Wilson IA, Wyatt R.A Blueprint for HIV Vaccine Discovery. Cell Host Microbe. 2012 Oct 18;12(4):396-407. doi: 10.1016/j.chom.2012.09.008.

7. Auvert B, Taljaard D, Lagarde E, Sobngwi-Tambekou J, Sitta R, Puren A. Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: the ANRS 1265 Trial. PLoS Med. 2005 Nov;2(11):e298. Epub 2005 Oct 25. Erratum in: PLoS Med. 2006 Mai;3(5):e298.

8. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, Hakim JG, Kumwenda J, Grinsztejn B, Pilotto JH, Godbole SV, Mehendale S, Chariyalertsak S, Santos BR, Mayer KH, Hoffman IF, Eshleman SH, Piwowar-Manning E, Wang L, Makhema J, Mills LA, de Bruyn G, Sanne I, Eron J, Gallant J, Havlir D, Swindells S, Ribaudo H, Elharrar V, Burns D, Taha TE, Nielsen-Saines K, Celentano D, Essex M, Fleming TR; HPTN 052 Study Team Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med. 2011 Aug 11;365(6):493-505. doi: 10.1056/NEJMoa1105243. Epub 2011 Juillet 18.

9. Hütter G, Nowak D, Mossner M, Ganepola S, Müssig A, Allers K, et al. Long-term control of HIV by CCR5 Delta32/Delta32 stem-cell transplantation. N Engl J Med. 2009 Fév 12;360(7):692-8.

10. Katlama C, Deeks SG, Autran B, Martinez-Picado J, van Lunzen J, Rouzioux C, et al. Barriers to a cure for HIV: new ways to target and eradicate HIV-1 reservoirs. Lancet. 2013 Mar 28. doi:pii: S0140-6736(13)60104-X. 10.1016/S0140-6736(13)60104-X.

11. Insurability of HIV-positive people treated with antiretroviral therapy in Europe: collaborative analysis of HIV cohort studies. Josee Kaulich-Bartz, Wayne Dam, Margaret T. May, Bruno Lederberger, Urs Widmer, Andrew N. Phillips, Sophie Grabar, Amanda Mocroft, Josep Vilaro, Ard van Sighem, Santiago Moreno, Francois Dabis, Antonella D'Arminio Monforte, Ramon Teira, Suzanne M. Ingle, Jonathan A.C. Sterne, Writing Committee for the Antiretroviral Therapy Cohort Collaboration AIDS 2013, 27:1641–1655.

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