

Activity
report *2015-2016*

The ANRS was created in 1988.

It brings together researchers from different fields and institutions in the developed world and in resource-limited countries to study scientific questions. The ANRS funds research projects approved by international expert committees. It oversees projects from conception to completion and ensures that the results are used for the benefit of the populations concerned.

In 2012, the ANRS became an autonomous agency of Inserm (French National Institute of Health and Medical Research).

Contents

EDITORIAL	2
------------------	---

KEY FIGURES 2016	8
-------------------------	---

BASIC RESEARCH

Highlights	12
------------	----

Publications	14
--------------	----



CLINICAL RESEARCH

Highlights	28
------------	----

Publications	32
--------------	----



PUBLIC HEALTH AND PREVENTION RESEARCH

Highlights	46
------------	----

Publications	48
--------------	----



VACCINE RESEARCH

Highlights	56
------------	----

Publications	58
--------------	----



VALORIZATION AND TRANSFER

Transmission and communication	62
--------------------------------	----

Bibliometric analysis	67
-----------------------	----



MEANS

Human and financial means	70
---------------------------	----

ANRS organization	77
-------------------	----

Committees	78
------------	----



The quality of its research has raised the visibility of the ANRS



Professor Jean-François Delfraissy takes stock of the twelve years he spent as Director of the ANRS.

What do you consider to be the outstanding achievements of the ANRS over the last two years?

The agency's work on early treatment and prevention of HIV infection seems to me to have been decisive, because it holds out the hope that we can limit the epidemic, in both the developed world and resource-limited countries. I'm thinking in particular of the results of the TEMPRANO trial on immediate treatment of infected people. These results were published in the *New England Journal of Medicine* and led to a revision of the World Health Organization (WHO) treatment guidelines in resource-limited countries. Then there was the roll-out in South Africa and the results of TasP (Treatment as Prevention), the first large-scale trial on this strategy. Not to mention the IPERGAY findings on pre-exposure prophylaxis which were a major event. And there was research on rapid tests and self-testing. I think I can say that like this the ANRS became a major international player in research in the main fields concerning prevention.

The HIV Cure program on viral reservoirs and lasting HIV remission also seems to me paramount. The agency has defined a strategic vision regarding these questions and has given itself the means to implement it, notably by establishing a public-private partnership with MSD Avenir, in the framework of the ANRS-RHIVIERA consortium, which now has a solid network of teams that are international leaders in HIV remission, in basic and clinical research, and in primate models. In terms of these models, the creation of the IDMIT (Infectious Diseases Models for Innovative Therapies) is a prime asset. The recent publication in *Nature* of the fundamental research directed by Moncef Benkirane on the identification of a biomarker of cell HIV reservoirs illustrates the dynamic nature of this field of research.

Lastly, the ANRS supported the therapeutic revolution of direct-acting antivirals used to treat hepatitis C. Thanks to the cohorts we put in

place, in particular HEPATHER, we are able to observe what happens in “real life” with these drugs. There are many questions on the medium- and long-term effects of direct-acting antivirals: their side effects, potential interaction with the immune system, the progression of fibrosis and of cirrhosis after eradication of the virus, the incidence of hepatocarcinoma, and so forth. We have equipped ourselves to gather accurate information on all these points, and on patient outcome, notably among disadvantaged populations.

What are your main reasons for satisfaction after twelve years at the head of the ANRS?

In the first place, there is the consolidation of basic research, notably in recent years. In this regard, I ensured that scientific development was boosted and enabled new ways of funding through public-private partnerships, which until then had been very insufficient in basic research. My second reason for satisfaction concerns, as we have seen, research in prevention. When I took over as director, Bertran Auvert, supported by the ANRS, had just shown the value of circumcision. We were then in a position to demonstrate this benefit in a population in South Africa. This was a real advance. Subsequently, a great deal of research was undertaken worldwide on microbicides. I could be criticized for not have committed the ANRS to this research, but I considered that we had neither the teams nor the wherewithal to undertake research of sufficient quality. On the other hand, I saw that pre-exposure prophylaxis could be an interesting strategy. I supported IPERGAY, which was coordinated by Jean-Michel Molina. It was a risk, but it paid off. Now, in all international meetings on prevention, the opinion of the ANRS is sought and respected. Lastly, the collaboration between basic researchers and clinicians remains, in my eyes, a priority. Long-term controllers are a successful example of this.

Do you think that the role played by the ANRS was sufficiently decisive in hepatitis?

I think that we have played an important part, and should continue to do so. The financial commitment of the ANRS to hepatitis was notably increased. Work on hepatitis accounted for 5% to 6% of the agency’s budget when I arrived. Some years, we earmarked 30% of the budget for hepatitis. We were unable to contribute to therapeutic research on hepatitis C to the same extent as we did on HIV, simply because the

Editorial

therapeutic revolution happened in less than three years and was validated by industry. Our strategic choice was to set up cohorts promptly to address outstanding questions on direct-acting antivirals. These cohorts notably contributed to the ministerial decision regarding universal access to these drugs. Furthermore, our program HBV Cure on hepatitis B was one of the first in the world on this scale. I think I can say that the ANRS plays an important role in viral hepatitis research.

What about research in resource-limited countries?

My predecessor, Michel Kazatchkine, prioritized involvement of the ANRS in resource-limited countries. This was decisive in drawing up and implementing the agency's research policy in resource-limited countries. I sought to continue and amplify this, notably by favoring inter-site studies and trials and by setting up international partnerships with, for instance, the European & Developing Countries Clinical Trials Partnership and the Bill & Melinda Gates Foundation. Above all, it seemed to me essential to transform the ANRS sites into open research platforms with the means and personnel to forge partnerships and undertake multicenter research. These platforms also became more multipurpose. If further proof were needed, there is our experience with the Ebola epidemic. The sites in Ivory Coast, Senegal, and Cameroon, in the framework of the Inserm REACTing program, enabled us to respond effectively to this epidemic. Even though this was a lot of work, these platforms adapted quickly to the new situation, by virtue of know-how and expertise acquired through their work on HIV and hepatitis. The ANRS sites now constitute what I consider to be an extremely precious worldwide network. This is a model we showed could be extended to other subjects, notably infectious diseases, but also metabolic diseases, for example. The future will probably be to "merge" to a greater extent research in the developed world and in resource-limited settings.

Have relations with patient groups evolved as you would have wished?

When a research institution joins forces with a patient group, it happens in three stages. First discussion, followed by the forging of partnerships around research projects, and lastly joint research. The ANRS is at stage three of this process and I believe that we are the most advanced in France in this regard. We managed to do genuinely community research, in which the patient groups are direct stakeholders. This was

so with the IPERGAY trial, which we wouldn't have been able to perform without the association AIDES. Everything we undertake in terms of prevention in the different target populations is done with the involvement of the patient groups concerned. This is not always so simple, as a joint learning process is needed, but I feel it is essential to put civil society at the heart of research.

Why did you undertake restructuring of the HIV vaccine program?

In conjunction with Professor Yves Lévy, the director of the vaccine program at that time, I decided to take the vaccine program out of the ANRS and to create a separate facility, the Vaccine Research Institute (VRI). Like the creation of the Vaccine Research Center alongside the National Institute of Allergy and Infectious Diseases in the United States. We made this strategic choice because of the complexity associated with the setting up of a vaccine program. Vaccine research is incompatible with the funding of successive projects. Making a vaccine takes time. The commitment must be lasting. The VRI at the outset received substantial forward-looking investment. It comprises research teams from most scientific institutions, and so really took off. The VRI still receives funding from the ANRS, but also now from other sources, notably the European Union.

Are you satisfied with the agency's international standing?

The agency was already held in high regard before I arrived, but I think we've gained in visibility since. We are present in all the important international bodies – WHO, Unitaïd, UNAIDS, etc. –, and our role is fully acknowledged. This visibility has also increased nationally since we have influenced some major public health decisions, such as the temporary recommendation for use and then the marketing authorization of Truvada® for pre-exposure prophylaxis of HIV and universal access to direct-acting antivirals for treatment of chronic hepatitis C. Lastly, the agency's publication output means that France is second or third in the world. This is the standing that has led the ANRS to co-organize the 9th International AIDS Society (IAS) Conference in July 2017 in Paris.

Do you consider that the incorporation of the ANRS into Inserm was a good thing?

Overall yes, because we would have been in a weaker situation in terms of critical mass had we remained a public interest group (GIP) rather

Editorial

than joining Inserm. Various positive interactions have been initiated in terms of human resources, management, and pharmacovigilance, for example. That said, I will be fully confident in this decision the day when the ANRS is transformed into a large infectious diseases institute, a progression that clearly makes sense.

In personal terms, was it difficult for you to leave the ANRS?

I was ready to leave one day or another! Twelve years, it's still a long time, even though I'm way behind Tony Fauci who beats all records at the head of the National Institute of Allergy and Infectious Diseases in the United States! It's natural that there's renewal, new visions, and I'm really pleased to be handing over the directorship of the agency to François Dabis, a leading scientist. What's more, I'm leaving at a time when, it seems to me, the ANRS is doing well scientifically and organizationally. So, although it wasn't necessarily easy, my leaving hasn't been painful. Furthermore, as chance would have it, I find myself at the head of a prestigious institution, the National Consultative Ethics Committee, which is just as exciting.

PR JEAN-FRANÇOIS DELFRAISSY
Director (2005-2017)

François Dabis

New director of the ANRS



**Pr François Dabis,
new director
of the ANRS**

Appointed director of the ANRS on 22 March 2017, François Dabis is a university professor and hospital physician, and is well known in the HIV/AIDS research community. As an epidemiologist and public health specialist, Professor Dabis has put in place and directed large cohorts of HIV-infected patients in France – the ANRS CO 03 cohort, with 30 years of follow-up, and, over the last 12 years, cohorts of patients infected by HCV and HIV (ANRS CO13 HEPAVIH) – and in West Africa, where his work has brought him international recognition.

Professor Dabis headed ANRS 049 DITRAME, the trial which in 1999 provided proof of the efficacy of short AZT treatment in reducing mother-to-child HIV transmission in West Africa. More recently, with his South African colleagues, Professor Dabis has sought to evaluate the efficacy, in a region greatly affected by HIV infection, of an original approach combining repeated offers of home-based screening and rapid medical treatment of all those infected. The first results of ANRS 12249 TasP have revealed the difficulties of implementing such an approach in the field and do not provide conclusive evidence of short-term reduction in the risk of HIV transmission in the population.

Professor Dabis was president of ANRS coordinated action AC12 – Research in resource-limited countries – from 2002 to 2015. He was a member of several WHO and UNAIDS expert committees tasked with drawing up international directives on HIV/AIDS. He coordinated the setting up of RIPOST, an initiative designed to strengthen the capacity of national public health institutes in West Africa to respond to epidemic threats.

Professor Dabis was president of the Scientific Boards of InVS (French Institute for Public Health Surveillance, now Public Health France) from 2003 to 2012, and a member of HCSP (French public health board) from 2011 to 2016.

Key figures 2016

Budget

- € **50.176** million of open credits
- 94 %** of the budget is devoted to the funding of research
- € **12** million for staff, with
- 260** posts for doctoral students, post-docs, monitors for clinical, laboratory, and social sciences studies, and personnel working on research

Research funding

- 205** research proposals received,
- 83** selected,
- 119** research grant applications,
- 40** selected

Personnel

- 55** people at the ANRS main office
- 504** projects ongoing,
- 382** of them from calls for proposals

HIV/AIDS basic research

- 15.8 %** of expenditure
- 145** projects and grants ongoing

HIV vaccine research

- 12.6 %** of expenditure
- 35** projects and grants ongoing

HIV/AIDS clinical and therapeutic research

- 26.1 %** of expenditure
- 65** projects and grants ongoing

Public health, human and social sciences research

4.4 % of expenditure
43 projects and grants ongoing

Basic and clinical research on viral hepatitis

22.8 % of expenditure
116 projects and grants ongoing

Research in resource-limited countries

16.6 % of expenditure
74 projects and grants ongoing

Clinical studies in France

The ANRS is sponsoring **62** ongoing clinical studies in France

Over **32 000** patients, **19 800** of them in the HEPATHER cohort

1 global network of over **300** hospital departments,

6 monitoring and data analysis center

1 centralized biobank

1 biobank dedicated to HEPATHER

Publications

512 scientific publications in 2016 from projects funded
by the ANRS, half of them in journals with an impact factor >5.

Basic research



Highlights

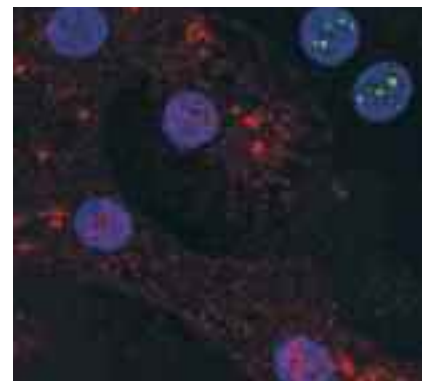
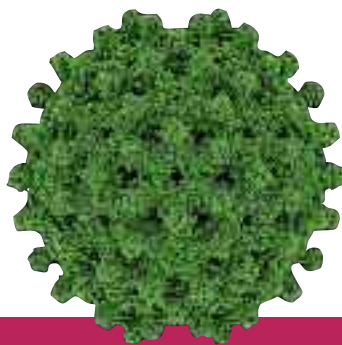


A symposium on new technologies

The ANRS organized on 4 and 5 October 2016 at the Institut Pasteur in Paris an international symposium on new technologies applied to HIV research, which was attended by 250 participants. The aim was to explore the varied landscape of today's new technologies, both in terms of their development and applications, and to promote interaction between researchers of different disciplines, including those outside HIV research, to drive forward HIV/AIDS research.

A partnership for the ANRS-RHIVIERA consortium

Created in 2014, the ANRS-RHIVIERA consortium mobilizes resources and collaborations for innovative research programs on remission of HIV infection. This consortium can also seek private funding and a partnership contract was thus concluded in March 2015 with MSD Avenir. This contract in particular supports funding of pVISCANTI, a study which uses nonhuman primate models at IDMIT (Infectious Diseases Models for Innovative Therapies). This study is seeking to understand the balance between the immune response and viral reservoirs, an equilibrium necessary for achieving long-term remission of HIV infection. This partnership will open up to other industrial partners.



TOWARDS A CURE FOR HEPATITIS B: SPECIFIED AIMS

With 240 million patients affected worldwide, chronic hepatitis B, despite a prophylactic vaccine and some curative treatments, remains a major public health problem. The ANRS is a major stakeholder in the fight against this disease, through its support of research projects, but also its program HBV Cure. In June 2014, an international seminar reviewed the state of the art in basic and clinical research. Today's and tomorrow's great challenges include understanding the different stages of the life cycle of the virus, including its entry in hepatocytes, formation of the viral mini-chromosome and of virions, interactions with the immune system, and identification of biomarkers to monitor disease progression and to develop new more effective antivirals. The aim is to develop therapeutic strategies to eradicate HBV.

Zeisel MB, Lucifora J, Mason WS et al. Towards an HBV cure: state-of-the-art and unresolved questions--report of the ANRS workshop on HBV cure. Gut. 2015; 64 (8): 1314-26. doi: 10.1136/gutjnl-2014-308943.

HBV Cure: gaining momentum

In recent years, the ANRS has gained momentum in driving research on hepatitis B, notably through the creation of coordinated action 34 (AC34) and its program HBV Cure. The main aim is to identify new therapeutic targets by a coordination of basic, translational, and clinical research. AC34 organizes an annual international workshop, the second and third of which were held in Paris in 2015 and 2016. They brought together all international teams involved in hepatitis B research, the status of which was reviewed. The third workshop also saw the launch of ICE-HBV (International Coalition to Eliminate Hepatitis B Virus), which is designed to consolidate international cooperations.



ICE-HBV: INTERNATIONAL MOBILIZATION AGAINST HBV

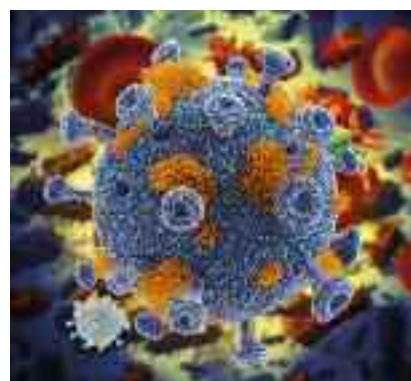
To find innovative treatments to cure HBV infection, there is an urgent need for a coordinated international strategy bringing together researchers and clinicians, and involving patients and members of institutions. In an opinion piece published in *Nature Reviews* that takes stock of our understanding and of current treatments, the authors propose, as was done for HIV, the establishment of an International Coalition to Eliminate the Hepatitis B Virus (ICE-HBV). The aim is global eradication of HBV infection in the next 30 years.

Revill P et al. Global strategies are required to cure and eliminate HBV infection. Nat Rev Gastroenterol Hepatol 2016; 13 (4): 239-48. doi: 10.1038/nrgastro.2016.7.

New priorities of basic research on HCV

In the context of the therapeutic innovation provided by direct-acting antivirals, in 2016 the ANRS, together with the French community involved, looked into the future of basic research on HCV. Four subjects seemed to be priorities: HCV and metabolic alterations, HCV and hepatocellular carcinoma, HCV and vaccines, and HCV as a model for research on other viruses.

This review led to the planned creation in 2017 of a working group on Virus-Induced Carcinogenesis (HBV-HCV), and of a new coordinated action "Lipid metabolism and HCV." HCV hijacks and controls certain pathways of lipid metabolism, probably to optimize its infectious cycle. The metabolic alterations induced contribute to acceleration of hepatic fibrosis and to development of hepatocellular carcinoma. HCV is an exemplary model of the manipulation of cell metabolism by a virus, and it is important to shed light on this manipulation.





Publications



Publications from ANRS-funded basic research on HIV, HBV, and HCV reflect the drive and excellence of the research teams. Strategic international partnerships heighten the response of teams that take on new challenges.

Viral load (partly) under control of the major histocompatibility complex

HIV is sensitive to variations in its environment and host genetic polymorphism influences viral load and hence disease progression. But the mapping of the regions of the human genome involved, using studies of pangenomic associations, has never been done. The analysis of some eight million genetic variants in more than 6000 European patients has revealed two important zones: the major histocompatibility complex (chromosome 6) and to a lesser degree the gene cluster on chromosome 3 coding for a chemokine receptor. While the major role of HLA, which determines the response of cytotoxic T cells, seems coherent, it would nevertheless be interesting to extend this analysis to other populations and other genetic variants.

McLaren PJ, Coulonges C, Bartha I et al. Polymorphisms of large effect explain the majority of the host genetic contribution to variation of HIV-1 virus load. Proc Natl Acad Sci USA 2015; 112 (47): 14658-63. doi: 10.1073/pnas.1514867112.



HIV controllers: what role for CD8+ T cells?

So-called HIV controllers (i.e. long-term nonprogressors or elite controllers) control HIV infection without treatment. Fortunate indeed, but the mechanisms remain mysterious. HIV controllers frequently have a specific HLA-B gene and show a strong CD8+ T cell response, which helps control the infection, but we do not know the exact role of this genetic protection of CD8+ T cells in the maintenance of this natural control. Experiments on temporary depletion in CD8+ T cells in a macaque SIV controller model seem to indicate that CD8+ T cells are not, in fact, directly involved, or in any case are not the only effectors, in the long-term maintenance of viral control. The other mechanisms involved have yet to be elucidated.

Bruel T, Hamimi C, Dereuddre-Bosquet N et al. Long-term control of simian immunodeficiency virus (SIV) in cynomolgus macaques not associated with efficient SIV-specific CD8+ T-cell responses. J Virol 2015; 89 (7): 3542-56. doi: 10.1128/JVI.03723-14.

HIV controllers: a highly effective T cell receptor repertoire

The capacity that some (rare) people have to control HIV naturally seems to result from a particularly effective immune response, the molecular underpinnings of which are worth studying. The T cell receptor (TCR) repertoire directed against Gag293, the major epitope of the viral capsid recognized by the CD4+ T cells of these HIV controllers, thus reveals a predominance of TRAV24 and TRBV2 variable genes and of clonotypes producing TCRs with high degrees of affinity. This hypersensitivity is regulated by several HLA-DR alleles, is transmitted by transfection to healthy donor CD4 cells, and redirects CD8+ T cells to the HIV-1 capsid. The transfer of these "superclonotypes" could inspire new immunotherapeutic approaches.

Benati D, Galperin M, Lambotte O et al. Public T cell receptors confer high-avidity CD4 responses to HIV controllers. J Clin Invest 2016; 126 (6): 2093-108. doi: 10.1172/JCI83792.

The impact of HIV on T follicular helper cells

The spleen, half of which is composed of B cells, is a key element in the activation of the humoral immune response. But the role in the spleen of T follicular helper (Tfh) cells, which are essential to B cells in the production of antibodies, has hitherto been little studied during HIV or SIV infection. In SIV-infected rhesus macaques there is a dramatic loss of splenic Tfh cells at the acute phase of infection. This decrease is associated with a decline in memory B cells and with a change in the architecture of the lymph tissue. The splenic Tfh cells are, moreover, infected by the virus and could constitute a viral reservoir. These discoveries help explain the weakness of the humoral response to HIV/SIV, and also open a way to new therapeutic and vaccine approaches.

Moukambi F, Rabezanahary H, Rodrigues V et al. *Early loss of splenic Tfh cells in SIV-infected rhesus macaques*. PLoS Pathog 2015; 11 (12): e1005287. doi: 10.1371/journal.ppat.1005287.



HIV-2 controlled by CD8 T cells

In people infected by HIV-2, the disease rarely progresses, even without treatment. In the cohort of the study ANRS IMMUNOVIR-2 and the cohort ANRS CO5 HIV-2, this viral control stems from a large and lasting stock of CD8 T cells, which are able to eliminate the cells of the body that harbor the virus. Better understanding of the exact mechanisms of this "virtuous circle," which works against the propagation of HIV-2, could help develop therapeutic leads regarding HIV-1, against which the body's immune resources are quickly exhausted, thus favoring replication of the virus.

Angin M, Wong G, Papagno L et al. *Preservation of lymphopoietic potential and Virus suppressive capacity by CD8+ T cells in HIV-2-infected controllers*. J Immunol 2016; 197: 2787-95. doi: 10.4049/jimmunol.1600693.

CXCL10/IP-10, predictor of the progression of HIV infection

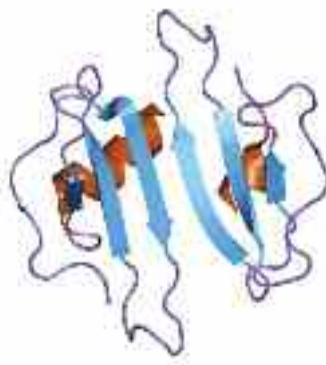
Chronic inflammation is a major characteristic of HIV infection and has implications in terms of viral persistence and clinical manifestations. In analyzing four human cohorts as well as primates at different stages of infection, it appears that a high level of the chemokine CXCL10/IP-10 before infection is associated with faster progression of the infection. Furthermore, the production of IP-10 is located in the intestine and is correlated with the number of cells infected. The IP-10 receptor is strongly expressed on memory CD4+ T cells. So, in addition to its utility as a predictor of disease progression, CXCL10/IP-10 sheds light on the mechanisms of formation of viral reservoirs.

Ploquin MJ, Madec Y, Casrouge A et al. *Elevated basal pre-infection CXCL10 in plasma and in the small intestine after infection are associated with more rapid HIV/SIV disease onset*. PLoS Pathog 2016; 12 (8): e1005774. doi: 10.1371/journal.ppat.1005774.

Broadly neutralizing antibodies against HIV

Broadly neutralizing antibodies, which block the entry of the virus in target cells, are at the heart of numerous studies and of many therapeutic expectations. While the mechanisms of action are not yet fully elucidated, this study shows that some broadly neutralizing antibodies are able to induce the destruction of HIV-1-infected cells by natural killer cells. This mechanism of antibody-dependent cellular cytotoxicity requires lasting binding of the antibodies to the protein envelope of HIV-1. While the sensitivity, and so the killing potential, of these broadly neutralizing antibodies varies according to the viral strain, these recent data on the parameters that control the cytotoxic action of these antibodies could help to optimize their use in the eradication of viral reservoirs.

Bruel T, Guivel-Benhassine F, Amraoui S et al. *Elimination of HIV-1-infected cells by broadly neutralizing antibodies*. Nat Commun 2016; 7: 10844. doi: 10.1038/ncomms10844.





questions to...

**Professor
Roger Le Grand,
executive director
of Infectious
Diseases Models
for Innovative
Therapies (IDMIT)**



PRECLINICAL RESEARCH: “WE HAVE SCALED UP!”

Once fully operational, IDMIT will be the largest European institution of preclinical research on human infectious diseases. How and why was IDMIT created?

At the creation of the ANRS, preclinical research on HIV was important. The different teams involved, over several sites, developed internationally recognized expertise in this field. Ten years ago, we faced two challenges. First, there was an urgent need for research into Chikungunya virus and so for a diversification of our activities. Second, it was necessary to meet the increasing needs of the scientific community and so remain competitive in the medium term and internationally. The ANRS strongly supported us at the time by exploring the idea of a coordinated preclinical research network. This boost was seminal. It led us to build a joint project for all organizations and institutions involved, to wit, the CEA, the ANRS, Inserm, University Paris-Sud, and the Institut Pasteur, and to apply for funding within the framework of the investments in the future program. We thus obtained in 2011 and 2012 €27 million for equipment and infrastructure. A building is nearing completion. The aims are to have a centralized site, at Fontenay-aux-Roses, which accommodates all expertise and skills, offers the best research possibilities, and leads to gains in productivity. IDMIT has privileged scientific relations with the Vaccine Research Institute.

What capacity and equipment will IDMIT have and what will be your activities?

We will have a building with about 10 000 m² floor space, including 1800 m² for laboratories. The building will be fitted out with the latest equipment, will have animal facilities for 530 nonhuman primates, and will accommodate up to 110 scientists and technicians. With these means, approximately half of our activities, which are already partly underway, will be focused on HIV. At the same time, we are developing programs on influenza, dengue fever, Chikungunya virus, Zika virus, and vaccination against Ebola, whooping cough, and chlamydiosis. Most of these research programs are supported by academic partnerships funded notably by the European Union, the ANRS, and the French National Research Agency.

How do you address animal welfare?

The question of animal welfare is a legitimate social concern, which we address in several ways. First, through the greatest possible transparency in our activities. Then, by improving our experimental methodologies, so as to use as few animals as possible and to minimize invasiveness. Lastly, by developing research designed to determine the experimental conditions that best protect animal welfare. This is a requirement relevant not only to animal care, but also to the quality of research. It has been shown, for example, that animal stress can affect the biological results of experiments.



SAMHD1, Vpx, and the viral capsid

Identified in 2011, SAMHD1 is a restriction factor which limits the capacity of HIV-1 to infect dendritic cells, notably by denying it the nucleotides it needs to replicate.

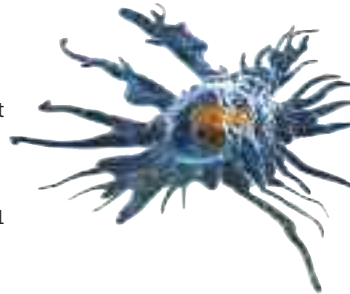
But certain lines of the virus, including HIV-2 and simian immunodeficiency virus (SIV), have developed a viral protein, Vpx, which degrades SAMHD1. By using chimeric viruses and varying different factors, the infection of dendritic cells is seen to be regulated not only by SAMHD1 and Vpx, but also by the viral protein of the capsid. This information sheds new light on the complex gymnastics that primate lentiviruses have developed during evolution to infect dendritic cells.

Barateau V, Nguyen XN, Bourguillault F et al. The susceptibility of primate lentiviruses to nucleosides and Vpx during infection of dendritic cells is regulated by CA. J Virol 2015; 89 (7): 4030-4. doi: 10.1128/JVI.03315-14.

HLTF: a newly identified target for Vpr

HIV-1 and HIV-2/SIV interact with the DNA repair system, but have developed different strategies to circumvent and counter host mechanisms. So, if HIV-2/SIV targets SAMHD1 thanks to Vpx and deprives the host cell nucleotides, HIV-1 depends on the degradation by Vpr of HLTF, a DNA-translocase involved in the repair of replication forks and maintenance of genome integrity. This recent discovery, obtained by quantitative proteomic analyses, unveils a new defense mechanism of HIV-1 against the defensive strategies of the host cell, while revealing a hitherto unknown restriction model. The degradation of HLTF highlights the hypothesis of a new way HIV interferes with the immune response, in which DNA-translocases seem to play a role.

Lahouassa H, Blondot ML, Chauveau L et al. HIV-1 Vpr degrades the HLTF DNA translocase in T cells and macrophages. Proc Natl Acad Sci USA 2016; 113 (19): 5311-6. doi: 10.1073/pnas.1600485113.



Dendritic cells are essential in countering the retrovirus

On infection by a retrovirus, the virus, upon entry into the cytoplasm, is acted on by a defense mechanism called restriction, operated notably by TRIM5 α . Now, in the dendritic cells of nonhuman and human primates, TRIM5 α is inoperative because it is sequestered in the nucleus (in the Cajal bodies) following its modification by SUMOylation. Paradoxically, this loss of antiviral restriction leads to effective detection of entering retroviruses by the pathogen receptors of dendritic cells, thus triggering an alert in the body. This mechanism, which is specific to dendritic cells, illustrates their capacity to adapt their response to viral attacks and their polyvalence at the frontier between innate and adaptive immunity.

Portilho DM, Fernandez J, Ringeard M et al. Endogenous TRIM5 α function is regulated by SUMOylation and nuclear sequestration for efficient innate sensing in dendritic cells. Cell Rep 2016; 14 (2): 355-69. doi: 10.1016/j.celrep.2015.12.039.

A subversive messenger in the immune response

Cellular defense mechanisms against viruses are complex. cGAMP, a derivative of cyclic guanosine monophosphate (GMP)-adenosine monophosphate (AMP) synthase (cGAS), is one of the messengers essential to the cascade of reactions. cGAMP adds a string to its bow: it can be packed in the cells and viral extracellular vesicles and delivered to dendritic cells, which trigger the adaptive immune response. In nature, this transmission of cGAMP by the virus appears to be a particularly subtle mechanism of propagation of the immune response from infected cells to cells not yet infected. It could be worth using this subversion of the virus for therapeutic or vaccine purposes.

Gentili M, Kowal J, Tkach M et al. Transmission of innate immune signaling by packaging of cGAMP in viral particles. Science 2015; 349 (6253): 1232-6. doi: 10.1126/science.aab3628.





Publications



Two cytokines with unexpected effects

The body deploys numerous mechanisms against HIV, but sometimes the immune system effectors themselves play the virus's game. Thus, the interleukins IL-2 and IL-7 induce phosphorylation – and so inactivation – of SAMHD1, a restriction factor which inhibits infection by HIV-1. IL-7 improves viral reverse transcription and integration into the host cell and may also play a crucial role in the constitution of viral reservoirs, by increasing the sensitivity of quiescent CD4+ T cells at infection. This deactivation of SAMHD1 is greatly reduced by treatment with dasatinib, a tyrosine kinase inhibitor used in oncology, which appears to be a potential therapeutic candidate, in addition to antiretroviral therapies, in prevention of the development of viral reservoirs at primary infection.

Coiras M, Bermejo M, Descours B et al. IL-7 Induces SAMHD1 phosphorylation in CD4 + T lymphocytes, improving early steps of HIV-1 life cycle. Cell Rep 2016; 14 (9): 2100-7. doi: 10.1016/j.celrep.2016.02.022.



The import and integration of HIV under the control of Nup 153 and Tpr

Lentiviruses hijack the cellular machinery of the host cell, but the molecular mechanisms whereby HIV enters the nucleus and is incorporated into the genome of the host cell are still unknown. Study of the nuclear pore shows that the nucleoporin Nup 153 is essential to the import of the virus and that nucleoporin Tpr depletion reduces infectivity, but not viral integration. This underpins the idea of concerted integration with the import of HIV, underlining a role of Tpr in the maintenance below the pore of a chromatin favorable to transcription of viral genes. While explaining some key stages of HIV infection, these results could also offer new insight into how host/pathogen interactions contribute to the establishment of HIV persistence.

Lelek M, Casartelli N, Pellin D et al. Chromatin organization at the nuclear pore favours HIV replication. Nat Commun 2015; 6: 6483. doi: 10.1038/ncomms7483.

SUN2 and CypA: double agents in the service of HIV?

To ensure its multiplication, HIV must undergo reverse transcription, enter the cell, and be incorporated into the host genome, while protecting itself against innate immunity and antiviral factors. These include cyclophilin (CypA), which is one of the first proteins to bind to the viral capsid, but plays an ambivalent, incompletely elucidated role that is conserved between species. The restriction activity of CypA against the virus depends on the nuclear envelope protein SUN2, which is also essential for HIV infection of CD4+ cells and dendritic cells. An explanation of the respective roles of CypA and SUN2 helps clarify the molecular mechanisms underlying the first stages of HIV infection and the way the virus circumvents or hijacks the host's antiviral defenses.

Lahaye X, Satoh T, Gentili M et al. Nuclear envelope protein SUN2 promotes cyclophilin-A-dependent steps of HIV replication. Cell Rep 2016; 879-92. pii: S2211-1247 (16) 30363-1. doi: 10.1016/j.celrep.2016.03.074.



HIV integration and latency: count on LEDGF/p75

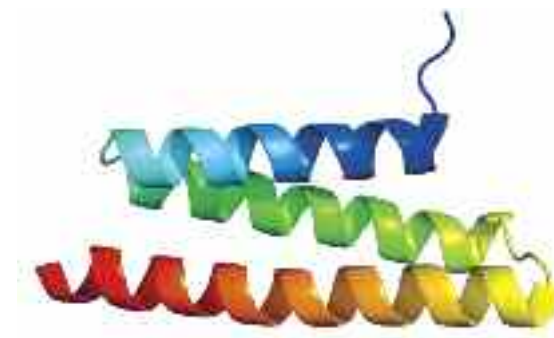
Understanding the mechanisms of viral latency is a major challenge in seeking to eradicate HIV. A complex of three subunits has just been identified: it combines LEDGF/p75 (a protein associated with the chromatin involved in DNA repair and gene expression control and which is necessary for preferential integration of HIV in activated cellular genes), *lws1* (a factor that controls transcription), and *Spt6* (a histone chaperone). The complex formed plays a role in the establishment and maintenance of the extinction of HIV in latently infected cells, because if it is destroyed, viral expression is reactivated. The protein LEDGF/p75, which is indispensable to viral integration, is also responsible, in combining with the proteins *lws1* and *Spt6*, for "post-integration" latency in viral reservoirs.

Gérard A, Ségéral E, Naughtin M et al. *The integrase cofactor LEDGF/p75 associates with lws1 and Spt6 for postintegration silencing of HIV-1 gene expression in latently infected cells.* Cell Host Microbe 2015; 17 (1): 107-17. doi: 10.1016/j.chom.2014.12.002.

First crystallographic structure of Vps4

ESCRT (endosomal sorting complexes required for transport) machinery is involved in numerous cellular processes, including the budding of HIV-1, and brings into play AAA-ATPase Vps4, which is highly conserved but poorly characterized. For the first time, the crystallographic structure of VPS4, a ring-shaped protein, has been solved. This will shed light on the conformational changes associated with the enzymatic activity of this asymmetric pseudo-hexamer. This basic research points the way to the characterization of VPS4 associated with a substrate, which could clarify the mechanism of HIV infection and help us to envision future therapeutic applications.

Caillat C, Macheboeuf P, Wu Y et al. *Asymmetric ring structure of Vps4 required for ESCRT-III disassembly.* Nat Commun 2015; 6: 8781. doi: 10.1038/ncomms9781.



Adipose tissue, an overlooked viral reservoir

What role does adipose tissue, the inflammatory potential of which is largely documented in obesity, play in characterized HIV infection, even treated, through the persistence of viral reservoirs and chronic inflammation? Analysis of adipose tissue from SIV-infected macaques and of HIV-infected patients treated with antiretrovirals shows that its composition is altered, with strong immune and inflammatory activation, and viral DNA able to replicate is present in macrophages and CD4+ T cells. So, adipose tissue constitutes a viral reservoir hitherto neglected that could be better targeted by treatments to limit viral persistence and chronic inflammation.

Damouche A, Lazure T, Avettand-Fénoël V et al. *Adipose tissue is a neglected viral reservoir and an inflammatory site during chronic HIV and SIV infection.* PLoS Pathog 2015; 11 (9): e1005153. doi: 10.1371/journal.ppat.1005153.

Origin of the group O of HIV-1

While the simian origin of groups M (the most extensive) and N among the four genetic variants of HIV-1 was identified several years ago, the reservoir of groups O and P was until now unknown. Using genetic analyses of fecal samples from gorillas in four African countries, an ANRS-supported international team has shown that these variants O and P originated by cross-species transmission from gorillas in south-west Cameroon. The origin of all the strains of HIV-1 circulating in humans is now elucidated.

D'arc M, Ayoub A, Esteban A et al. *Origin of the HIV-1 group O epidemic in western lowland gorillas.* Proc Natl Acad Sci USA 2015; 112 (11): E1343-52. doi: 10.1073/pnas.1502022112.



Publications



Basic research

HCV: lipid droplets under the control of septin

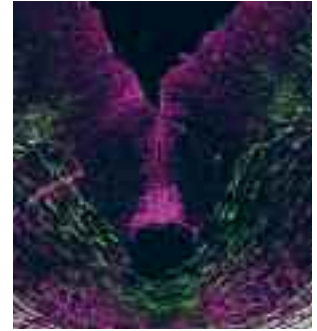
The accumulation of lipid droplets is characteristic of hepatitis C and is a major factor in steatosis, which can progress to cirrhosis and hepatocarcinoma. For the first time, a study has been performed of the role in the growth of lipid droplets of proteins of the septin family, which are involved in membrane stability and also carcinogenesis. In HCV-infected cells, septin 9 regulates, independently of HCV, the formation of lipid droplets by binding to PtdIns5P. In addition to a better understanding of the pathophysiology of hepatitis C, this unexpected function of septin 9 in the control of lipid homeostasis sheds new light on all diseases involving dysregulation of lipid metabolism.

Akil A, Peng J, Omrane M et al. Septin 9 induces lipid droplets growth by a phosphatidylinositol-5-phosphate and microtubule-dependent mechanism hijacked by HCV. *Nat Commun* 2016; 7: 12203. doi: 10.1038/ncomms12203.

Oxidative stress and HCV: the role of GPx4

Oxidative stress, which underlies inflammation and mutations, is involved in numerous diseases. In hepatitis C, HCV induces oxidative stress, but also scavenges reactive oxygen species (ROS). This paradoxical control of the intracellular level of free radicals was studied. The expression of glutathione peroxidase GPx4, which scavenges lipid peroxide, is augmented by HCV under the effect of NS5A and its extinction diminishes virion infectivity. GPx4 and other free radical scavengers could therefore be interesting targets for new therapeutic strategies intended to reduce viral replication and to treat the effects of oxidative stress, which induces hepatocarcinogenesis.

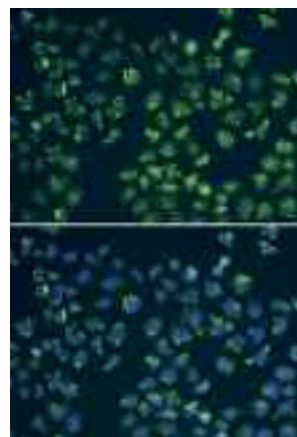
Brault C, Lévy P, Duponchel S et al. Glutathione peroxidase 4 is reversibly induced by HCV to control lipid peroxidation and to increase virion infectivity. *Gut* 2016; 65 (1): 144-54. doi: 10.1136/gutjnl-2014-307904.



New light on the oncogenic role of HCV via netrin-1

HCV is known to be a major factor in hepatocarcinoma, and the triptych virus/cancer/inflammation feeds a vicious circle. For the first time, the role of netrin-1, a protein overexpressed in numerous cancers and inflammatory diseases, has been studied in the context of HCV infection. Netrin-1 is positively regulated by the virus and, reciprocally, augments HCV infectivity. This double regulation involves UNC5A, the netrin-1 receptor, LARP1, and EGFR, a key element in the netrin-1-activated entry of the virus in the host cell. This positive feedback loop between HCV and netrin-1, along with EGFR, seems to be an important mechanism by which the virus establishes a lasting infection, which may, although this requires confirmation, lead to carcinogenesis.

Plissonnier ML, Lahlali T, Michelet M et al. Epidermal growth factor receptor-dependent mutual amplification between netrin-1 and the hepatitis C virus. *PLoS Biol* 2016; 14 (3): e1002421. doi: 10.1371/journal.pbio.1002421.





questions to...

Professor Jean-Michel Pawlotsky, director of the National Reference Center for hepatitis B, C, and D, and President of CSS 4 “Basic research in viral hepatitis” of the ANRS



“BASIC RESEARCH ON HCV MUST CONTINUE TO BE SUPPORTED”

In the context of the therapeutic revolution of recent years concerning hepatitis C, what are today’s great challenges in basic research on HCV?

The biology of HCV has yet to yield up all its secrets. The fact that we have drugs effective against a virus does not mean that research should grind to a halt overnight. So, work is ongoing on the rabies virus and the poliomyelitis virus. Furthermore, numerous studies need to be conducted on the mechanisms of diseases associated with HCV. In particular, I am thinking of carcinogenesis induced by this virus, notably of the liver. Liver cancer is increasingly frequent in HCV-infected patients, particularly older ones, including those cured of chronic hepatitis C. It is essential to decipher the direct role of the virus and the roles of inflammation and cirrhosis, and to understand how these respective factors are implicated. It is equally important to determine whether liver cancer in HCV-infected patients is similar to that in other patient populations or whether it has specific features, notably in terms of aggressiveness. Numerous other unanswered questions require continuation of basic research.

HCV is associated with non-liver diseases such as lymphomas and autoimmune diseases. Furthermore, HCV induces quite complex perturbations of carbohydrate and lipid metabolism. Lastly, I feel it is useful to maintain a technology watch, even though we can now cure most patients and have no immediate need for new drugs. If, for example, problems of major resistance arise, it will be useful to have continued to work on other fundamental approaches to HCV inhibition.

What other aims do you think we should pursue?

I believe that everything we have learned from HCV research, all the models and the technologies that have been developed, can be applied to other viral infections. In the same way as we were greatly inspired at the beginning of research into hepatitis C by the work done on HIV, we can now use HCV as a model for new approaches to the pathophysiology and inhibition of other viruses, in particular RNA viruses. In basic research, it is always important to have a model that has proven successful in testing hypotheses in closely related fields. HCV clearly constitutes an excellent model for a good many viral infections. This is a change of direction that all labs working on HCV are now following.

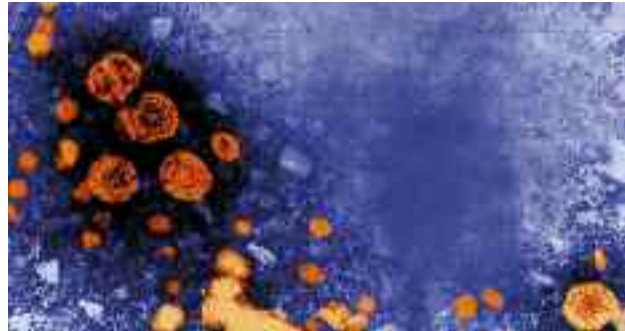
So, is it important to continue supporting basic research on HCV?

To imagine that we should shut up shop because we have succeeded in curing patients doesn’t seem reasonable to me, given what is at stake. France is home to very good research on HCV, with many important publications. We have a high-quality scientific network devoted to HCV and we need to enable this network to use all the experience accumulated with HCV for other applications.





Publications



Monensin inhibits HCV transmission

The exact mechanisms that regulate the entry and internalization of HCV in cells are unknown. It has recently been shown that monensin, an ionophore that induces an alkalization of intracellular organelles, inhibits the entry of HCV by blocking two viral transmission pathways: that of free viral particles and that of cell-to-cell transmission. Both pathways are pH-dependent. Mutants resistant to monensin have shown that the virus can develop pH-independent mechanisms of entry and have enabled us to define the critical role of HVR1 and ApoE as regulatory factors in HCV propagation. It would therefore be interesting to develop less toxic derivatives of monensin so as to envision therapeutic perspectives.

Fénéant L, Potel J, François C et al. New insights into the understanding of hepatitis C virus entry and cell-to-cell transmission by using the ionophore monensin A. J Virol 2015; 89 (16): 8346-64. doi: 10.1128/JVI.00192-15.

Detailed description of the HCV viral particle

HCV was identified in 1989, but we had to wait until 2016 for a description of the organizational structure of the viral particle, the highly infectious fraction that is rich in triglycerides, envelope glycoproteins, and apolipoproteins and which notably contains viral RNA. By direct immunocapture in electron microscopy, the ultrastructure of these lipoviral particles reveals a nucleocapsid surrounding and electron-dense nucleus that contains the viral genome and is surrounded by a lipid layer. It is interesting to note that this new morphological and organizational description obtained by electron microscopy confirms previous descriptions predicted from molecular biology data.

Piver E, Boyer A, Gaillard J et al. Ultrastructural organisation of HCV from the bloodstream of infected patients revealed by electron microscopy after specific immunocapture. Gut 2016. pii: gutjnl-2016-311726. doi: 10.1136/gutjnl-2016-311726.

Role of apolipoprotein E in the interaction of HCV with heparan sulfate

What factors and viral and cellular components condition the entry of HCV in the cell? We know that the structure of HCV bears similarities to that of a lipoprotein, and that the initial stages of its entry involves binding with polysaccharides like heparan sulfate.

Apolipoprotein E, one of the components of the virion, seems to be responsible for the binding of the virus to heparan sulfate. For binding between the virus and heparan sulfate, the latter must be sulfated in positions N and 6-O and must be at least a deca-saccharide. The envelope proteins at the surface of the viral particle are unable to ensure binding to heparan sulfate.

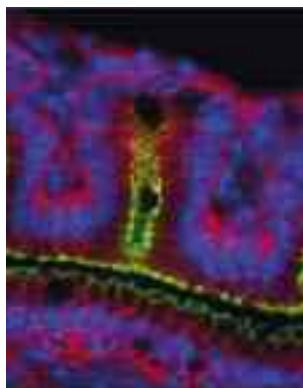
Xu Y, Martinez P, Séron K et al. Characterization of hepatitis C virus interaction with heparan sulfate proteoglycans. J Virol 2015; 89 (7): 3846-58. doi: 10.1128/JVI.03647-14.



HCV: a new therapeutic approach targeting claudin 1

Claudin 1 (CLDN1) is a liver protein of the “tight junctions” that is involved in the entry of HCV in liver cells. The idea of targeting claudin 1, to prevent and treat HCV infection, for which there is no vaccine, has proven relevant. In a transgenic mouse model, an anti-CLDN1 antibody blocked the entry of new virus and very rapidly eliminated cells already infected. By blocking CLDN1, this antibody inhibits the cellular signaling and interaction pathways needed by the virus for its spread and persistence. Very promising against HCV, this new therapeutic approach based on a claudin-1-targeting monoclonal antibody could be applied to other pathogens by using tight-junction proteins to infect their host.

Maily L, Xiao F, Lupberger J et al. Clearance of persistent hepatitis C virus infection in humanized mice using a claudin-1-targeting monoclonal antibody. Nat Biotechnol 2015; 33 (5): 549-54. doi: 10.1038/nbt.3179.



HCV does not infect hepatic stellate cells

Hepatic stellate cells play a key role in the development of liver fibrosis, one of the main complications of HCV infection. Although the interactions between hepatic stellate cells and HCV are poorly understood, a study has just established for the first time that HCV cannot infect or replicate in these cells, which do not express certain factors essential for the entry and production of viral particles. In the light of these new results, it seems therefore that chronic inflammation, together with the local immune response partly regulated by hepatic stellate cells, is mainly responsible for the liver fibrosis observed in HCV-infected patients.

Florimond A, Chouteau P, Bruscella P et al. Human hepatic stellate cells are not permissive for hepatitis C virus entry and replication. Gut 2015; 64 (6): 957-65. doi: 10.1136/gutjnl-2013-305634.

Boronic acid-modified nanocapsules block HCV entry

HCV, like HIV, is a virus with an envelope containing glycosylated proteins that play a role in the life cycle of the virus and in its entry in the cell. By blocking these envelope glycoproteins, with, for example, lectins, we may be able to prevent infection. A new generation of nanocapsules functionalized with amphiphilic boronic acid, which is known to bind to different glycans, has been developed and has proven effective in blocking viral entry at very low concentration. Stable and non-toxic, this new pseudo-lectin nanopeptide vector is a potent inhibitor of HCV entry, and opens the way to new anti-HCV therapeutic strategies.

Khanal M, Barras A, Vausselin T et al. Boronic acid-modified lipid nanocapsules: a novel platform for the highly efficient inhibition of hepatitis C viral entry. Nanoscale 2015; 7 (4): 1392-402. doi: 10.1039/c4nr03875d.



A new family of antivirals

The development of new broad-spectrum antivirals has become crucial. The cyclophilins, which are known to play a key role in the cell cycle of numerous viruses, but for which current inhibitors, cyclosporin analogs, have many drawbacks, appear to be interesting targets. Using fragment-based drug discovery, French researchers have created a new family of small non-peptide drugs which inhibit cyclophilins and are effective *in vitro* against HIV, HCV, and some coronaviruses. This new family of antivirals seems well suited to the requirements of clinical and industrial development and could have many other medical applications.

Ahmed-Belkacem A, Colliandre L, Ahnou N et al. Fragment-based discovery of a new family of non-peptidic small-molecule cyclophilin inhibitors with potent antiviral activities. Nat Commun 2016; 7: 12777. doi: 10.1038/ncomms12777.



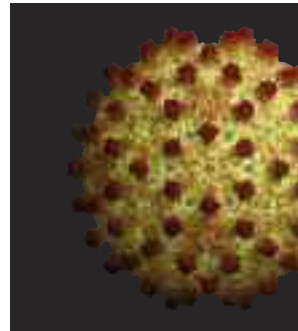
Publications



Ribavirin, a partly elucidated mechanism of action

Approved by the FDA in 1998, ribavirin, a nucleoside analog of guanosine with a broad antiviral spectrum, was widely used in anti-HCV treatment in combination with direct-acting antivirals and treatments based on interferon. To clarify the mechanisms underpinning its action, the effect of ribavirin on hepatocyte expression of genes activated by interferon (ISG) was studied. Ribavirin induced epigenetic modifications that led to reduced expression of ISG through conformational changes in chromatin and recruitment of the histone methyltransferase G9a. Ribavirin thus restores a hepatic environment sensitive to interferon in treated patients, whence the enhanced treatment efficacy.

Testoni B, Durantel D, Lebossé F et al. Ribavirin restores IFN α responsiveness in HCV-infected livers by epigenetic remodelling at interferon stimulated genes. Gut 2016; 65 (4): 672-82. doi: 10.1136/gutjnl-2014-309011.



HBV, a virus which inhibits the innate immune response

Although it has been little studied, how HBV interacts with hepatocytes in the first phases of infection sheds precious light on the reasons for the lack of efficacy of the local innate immune response. It appears that UV-resistant viral particles are able very early to inhibit the production of interferon by downregulating the expression of cytokine genes. These new findings help understand the mechanisms behind the establishment of chronic and persistent infection and explain the "stealthy" character of HBV. These findings are also precious in developing future therapeutic strategies targeting this repression of the innate immune response in the liver.

Luangsay S, Gruffaz M, Isorce N et al. Early inhibition of hepatocyte innate responses by hepatitis B virus. Antiviral Res 2016; 130: 36-45. doi:10.1016/j.antiviral.2016.03.008.

HBV: the mysteries of cellular transport

A virus of very distant origins, HBV has been studied for fifty years or so, but we still know little about how this circular DNA virus penetrates the host cell and releases highly infectious new virions. A 2016 review in *Journal of Hepatology* took stock of current understanding of the different stages of HBV infection, notably transport of the viral genome into the nucleus by means of the capsid, capsid disassembly, and the use of ESCRT machinery (endosomal sorting complexes required for transport) to catalyze budding and cross the membrane.

Blondot ML, Bruss V et Kann M. Intracellular transport and egress of hepatitis B virus. J Hepatol 2016; 64: S49-59. doi: 10.1016/j.jhep.2016.02.008.



HBSP, a better defined role

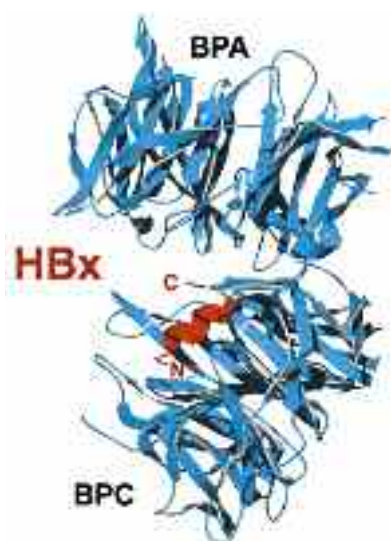
The recently discovered hepatitis B splicing-regulated protein (HBSP) is associated with a high proportion of defective HBV particles and the severity of liver disease in humans. To shed light on the phenomena of pathogenicity and viral persistence it therefore seems vital to elucidate the molecular role of HBSP, which is unknown. For the first time, it has been shown *in vivo* in a model of chronic liver inflammation that HBSP regulates cellular signaling pathways activated by TNF α and so limits hepatic inflammation. This hijacking of cellular signaling by TNF α seems to be one of numerous strategies developed by HBV to avoid the innate immune response.

Pol JG, Lekbaby B, Redelsperger F et al. *Alternative splicing-regulated protein of hepatitis B virus hacks the TNF- α -stimulated signaling pathways and limits the extent of liver inflammation.* FASEB J 2015; 29 (5): 1879-89.
doi: 10.1096/fj.14-258715.

Light on HBV transcription

To ensure its survival and genetic integrity, the genome of HBV remains in the nucleus of infected cells in the form of covalently closed circular HBV DNA (cccDNA), thus assuring its replication and the expression of viral proteins. By analyzing the structure of chromatin and its associated proteins during transcription or repression of transcription, it was shown that methylation or acetylation of histones regulated the transcription of cccDNA. The repression of transcription is notably characterized by condensation of chromatin and recruitment of HP1 and SETDB1. Expression of the viral protein HBx thwarts this repression and allows the establishment of active chromatin and the resumption of viral transcription.

Riviere L, Gerossier L, Ducroux A et al. *HBx relieves chromatin-mediated transcriptional repression of hepatitis B viral cccDNA involving SETDB1 histone methyltransferase.* J Hepatol 2015; 63 (5): 1093-102.
doi: 10.1016/j.jhep.2015.06.023.



Clinical research



Highlights



Evaluation of several treatment de-escalation strategies

In 2015, the ANRS launched three new trials exploring different strategies of de-escalation of antiretroviral treatment in patients with viral suppression. Two trials are assessing therapies combining an integrase inhibitor and a reverse transcriptase inhibitor (raltegravir + etravirine for ANRS 163 ETRAL, dolutegravir and lamivudine for ANRS 167 LAMIDOL). The ANRS 165 DARULIGHT trial is studying a triple-drug therapy with a protease inhibitor at half dose. The aim, through these treatment de-escalations, is to improve the quality of life of patients as well as their treatment adherence, while reducing the cost of treatment. The first results are expected in 2017.

HIV: two strategy trials

The ANRS has launched two new trials concerning anti-HIV treatment of adult patients in resource-limited countries. ANRS 12294 FIT-2 is an open trial assessing three first-line antiretroviral combinations in 210 HIV-2-infected patients. It has been running since early 2015 in five West African countries. Launched in November 2016 in three hospitals in Yaoundé in Cameroon, ANRS 12313 NAMSAL is comparing, in 600 treatment-naïve patients, the efficacy of an antiretroviral combination based on dolutegravir and the most frequently prescribed triple-drug therapy. Dolutegravir is an integrase inhibitor still inaccessible in most countries in sub-Saharan Africa.

Intermittent treatment: results of the ANRS 4D trial

The ANRS 162 4D trial has shown that intermittent antiretroviral treatment can be used in patients with viral suppression. This trial included 100 patients with a viral load undetectable for at least one year. They took classic triple-drug therapy 4 days a week instead of their continuous treatment. After 48 weeks of follow-up, viral suppression was maintained in 96% of them, with a satisfactory rate of adherence. This trial thus confirmed the proof of concept of this type of intermittent treatment.



A RANDOMIZED COMPARATIVE TRIAL OF INTERMITTENT TREATMENT

Following the positive results of ANRS 162 4D trial, the ANRS launched a comparative trial to evaluate the non-inferiority of intermittent antiretroviral treatment 4 days out of 7 compared with continuous treatment. This new trial, called QUATUOR, will include 640 patients with viral suppression divided into two groups for 50 weeks. After which, all patients will take intermittent treatment for nearly one year. QUATUOR is scheduled to start in mid-2017.



Prevention of mother-to-child HIV transmission using de-escalated treatment

The therapeutic strategy currently recommended for mother-to-child HIV transmission at pregnancy and at childbirth is particularly effective. But it was shown that children exposed to nucleoside analog reverse transcriptase inhibitors (NRTIs) may present mitochondrial abnormalities, sometimes leading to myocardial dysfunction. The ANRS thus rolled out in 2016 a trial to assess a preventive treatment without NRTIs. ANRS168 MONOGEST is aimed at pregnant women with viral suppression who until childbirth receive antiretroviral monotherapy with a boosted protease inhibitor (darunavir + ritonavir). The aim is to determine the feasibility and efficacy of such a strategy.



Two new cohorts

Two new cohorts will be set up in 2017. The first, ANRS CO24 ONCOVIHAC, will be used to assess the safety of anti-immune checkpoint antibodies in HIV-positive patients with cancer. The second, the international cohort iVISCANTI, will concern post-treatment HIV controllers. The cohort ANRS CO9 COPANA of patients not treated with antiretrovirals at inclusion was launched in 2004, and follow-up ended in 2016. For an example of a publication on this cohort concerning the effects on metabolism of late treatment, see page 33.

A trial in HCV-infected patients with treatment failure

Though highly effective, direct-acting antivirals do not cure chronic hepatitis C in all patients. The ANRS HC34 REVENGE trial was designed to evaluate a therapeutic strategy in patients with failure of a treatment combining two new direct-acting antivirals in a single tablet (grazoprevir/elbasvir), the direct-acting antiviral sofosbuvir, and ribavirin. This trial, which started in January 2016, concerns patients who carry genotype 1 or 4 HCV and is intended to determine the efficacy and safety of this "salvage" therapy.

Highlights



HEPATHER: other cohorts join

Officially launched in 2014 by the ANRS and the AFEF (French Association for the Study of the Liver), the national hepatitis cohort HEPATHER (ANRS CO22) was particularly successful in recruitment and by the end of 2016 included almost 21 000 patients. Following evaluation of all its cohorts, the ANRS decided to include the patients of cohorts CO12 CirVir and CO23 CUPILT in HEPATHER. This vast cohort, one of the largest in the world for this viral infection, was given a label of excellence in the framework of the investments in the future program of the ANR. Patients with hepatitis C or B in the chronic phase or cured will be followed up for approximately eight years. This is a unique source of data on viral hepatitis and is the subject of a public-private partnership with several pharmaceutical firms under the aegis of Inserm Transfert. The findings of this cohort were analyzed by the French health agencies to evaluate the efficacy and safety of these new drugs outside clinical trials. A partnership with the CNAM will provide answers to questions posed by the treatments in terms of medical economics.



Third-line: a cohort evaluating the strengthening of adherence

Launched in April 2013, the clinical cohort ANRS 12269 THILAO (Third-Line Antiretroviral Optimization) has been evaluating the strengthening of the adherence of patients with treatment failure who are receiving a second-line antiretroviral. In the event of a new failure, despite the intervention, the patients receive third-line treatment based on darunavir and raltegravir. The recruitment of 201 patients in Burkina Faso, Ivory Coast, Mali, and Senegal ended in May 2015. The data analysis is ongoing.

ANRS BIOBANKS

The largest French biobank is that of the ANRS, with over 1.8 million samples. This collection is an invaluable resource for research into new markers or new concepts. As its collaboration with the EFS (French blood transfusion service) was drawing to a close, the ANRS in 2015 requested proposals for new sample storage facilities. The biological resources center of the Bordeaux university hospital was selected and since April 2016 has centralized the computerized and physical storage of all samples for ANRS clinical studies. Inserm SC10 US019 continues to manage the logistics. This biobank is unique in size in France. The sole exception concerns the cohort ANRS CO22 HEPATHER, for which Cell&Co Bioservices, at Pont-du-Château (Puy of Dôme) is in charge of the management, coordination, and storage of samples. Since the end of 2016, the collections of the cohorts ANRS CO12 CIRVIR and ANRS CO23 CUPILT have been progressively incorporated into the facilities provided by Cell&Co Bioservices.

Surveillance of resistance to direct-acting antivirals

Although relatively rare, resistance to direct-acting antivirals is observed in approximately 5 to 8% of cases. To characterize and measure the incidence of resistance, a surveillance system was put in place in August 2015 in the national hepatitis cohort HEPATHER. This system concerns the patients in whom direct-acting antiviral treatment has failed or who have discontinued treatment prematurely, for whatever reason (adherence, adverse drug reactions, etc.).

HIV-tuberculosis coinfection: a phase 3 therapeutic alternative

The phase 2 trial ANRS 12180 REFLATE TB showed that raltegravir and efavirenz are of equivalent efficacy in triple-drug therapy, in patients coinfecting by HIV and tuberculosis, and determined the dose of raltegravir best adapted to this context. This result had, however, to be confirmed by a larger trial. The ANRS therefore launched in September 2015 the phase 3 trial ANRS 12300 REFLATE TB-2, which is comparing the same two triple-drug therapies in coinfecting patients. The plan is to include 460 patients in Brazil, Ivory Coast, Mozambique, and Vietnam.

STRENGTHENED COOPERATION WITH UNITAID

In 2016, two important partnerships were established between the ANRS and Unitaid, which has led to substantial financial support for two research projects. Launched in July 2016 in Cameroon, the trial ANRS 12313 NAMSAL is determining whether a simple and relatively inexpensive antiretroviral treatment based on dolutegravir can be used effectively in resource-limited countries. The second partnership relates to the three-year extension of the project OPP-ERA, the aim of which is to broaden access to effective and affordable tests of viral load, in West and Central Africa.

Hepatitis: two innovative trials

The ANRS in 2016 launched ANRS 12311 TAC, the first trial of a direct-acting antiviral against HCV in Central and West Africa. Conducted in Cameroon, Ivory Coast, and Senegal, the trial is evaluating the combination sofosbuvir + ledipasvir in 80 treatment-naïve patients presenting a genotype 1 or 4 HCV, and the genotype 2 patients receive sofosbuvir + ribavirin. In parallel, the ANRS started ANRS 12303 TOK in a district of Cameroon, a study designed to evaluate retrospectively the efficacy of routine vaccination against hepatitis B at birth in children born to mothers who screen positive for the antigen HBs.

Launch of the second phase of OPP-ERA

Measurement of viral load is essential for the follow-up of patients on antiretrovirals. OPP-ERA is designed to promote access to effective and affordable tests of viral load in four countries of West and Central Africa: Burundi, Cameroon, Ivory Coast, and Guinea. In the first phase, 76 000 tests were performed. On the back of this success, a second phase has since the fall of 2016 been progressively put in place to increase access to tests of viral load in the four countries concerned.





Publications



Clinical research on HIV and hepatitis in the developed world and in resource-limited countries has yielded noteworthy scientific publications over the last two years, some of which have led to changes to guidelines for patients care.

A low viral reservoir favors virological control upon discontinuation of antvirals

Is the level of viral DNA in the blood at discontinuation of antiretroviral treatment a good predictor of subsequent control of HIV? This is the question studied in ANRS 116 SALTO, in 95 patients treated early and whose viral load was below 400 copies/mL when antiretroviral treatment was stopped.

Conclusion: the patients with a low HIV-DNA level when their treatment was discontinued were better able to control the progression of the disease over a long period.

Assoumou L, Weiss L, Piketty C et al. A low HIV-DNA level in peripheral blood mononuclear cells at antiretroviral treatment interruption predicts a higher probability of maintaining viral control. AIDS 2015; 29 (15): 2003-7. doi: 10.1097/QAD.0000000000000734.



HIV-1 minority resistant variants have a limited impact on virological response in triple-drug therapy in highly pretreated patients

The ANRS 139 TRIO trial studied the prevalence of minority resistant variants (MRVs) at baseline of the trial and their impact on virological response. The combination of raltegravir, etravirine, and darunavir, combined with optimized treatment, was tested in patients harboring multiresistant viruses who were naive to these three drugs. A high level of MRVs was detected in these patients, but the study did not show that their presence was associated with a heightened risk of virologic failure, apart from a trend for patients exhibiting baseline etravirine MRVs.

Charpentier C, Lee GQ, Rodriguez C et al. Highly frequent HIV-1 minority resistant variants at baseline of the ANRS139 TRIO trial had a limited impact on virological response. J Antimicrob Chemother 2015; 70: 2090-6. doi: 10.1093/jac/dkv048.

Five drugs in primary infection are of limited interest

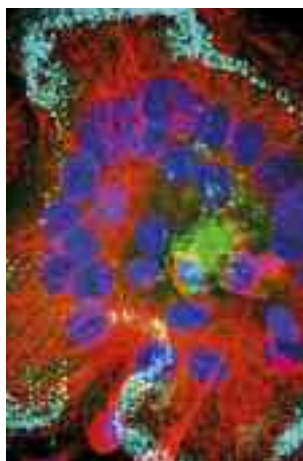
The use of combined antiretroviral therapy (cART) is recommended in France in the case of primary HIV infection, when the viral reservoirs are being established. The trial ANRS 147 OPTIPRIM has tested the efficacy of cART boosted by two other drugs, raltegravir and maraviroc, and compared it with standard cART using three drugs. After 24 months, this triple-drug therapy used in primary infection, which acts powerfully on viral reservoirs, showed no additional benefit when used in five-drug treatment including the two new drugs.

Chéret A, Nembot G, Mélard A et al. Intensive five-drug antiretroviral therapy regimen versus standard triple-drug therapy during primary HIV-1 infection (OPTIPRIM-ANRS 147): a randomised, open-label, phase 3 trial. Lancet Infect Dis 2015; 15: 387 – 96. doi: 10.1016/S1473-3099 (15) 70021-6.

Late treatment is associated with long-term inflammation and metabolic abnormalities

The immune deficiency induced by HIV is associated with metabolic abnormalities and systemic inflammation. Can antiretroviral therapy act on these? The immunological, metabolic, and inflammatory status of 208 patients of the cohort ANRS CO9 COPANA was followed up at initiation of treatment and three years later. Conclusion: a low CD4+ cell count at initiation of antiretroviral therapy, a sign of late treatment, is associated with high levels of insulin, triglycerides, IL-6, and hsCRP, which can contribute to an increased risk of cardiovascular and metabolic diseases.

Ghislain M, Bastard JP, Meyer L et al. *Late antiretroviral therapy (ART) initiation is associated with long-term persistence of systemic inflammation and metabolic abnormalities.* PLoS ONE 2015; 10 (12): e0144317. doi: 10.1371/journal.pone.0144317.



Intermittent therapy: influence on immunity, inflammation, and viral reservoir

The ANRS 141 TIPI trial in HIV-infected patients with a baseline CD4 level $\geq 500/\text{mm}^3$ who have yet to receive antiretroviral therapy, studied the clinical and biochemical changes induced by intermittent antiretroviral therapy. Two years of such treatment (alternating, 6 months with antiretroviral therapy and 6 months without) maintained the CD4 cell count above $500/\text{mm}^3$, without increase in the viral reservoir. Immune activation seems to be linked to replication of the virus, whereas inflammation evolves independently of other parameters and calls for specific attention.

Piroth L, Moinot L, Yéni P et al. *Immunity, inflammation and reservoir in patients at an early stage of HIV infection on intermittent ART (ANRS 141 TIPI Trial).* J Antimicrob Chemother 2016; 71: 490 – 6. doi: 10.1093/jac/dkv369.

HIV-1 replication in the male genital tract

Combined antiretroviral therapy significantly reduces the risk of sexual transmission of HIV. But although it controls plasma viral load, viral RNA can be detected in seminal fluid in men. To understand the underlying mechanisms, sperm from men who have sex with infected men who were in the trial ANRS EP49 EVARIST and on combined antiretroviral therapy was analyzed. The presence of viral DNA in the sperm cells was predictive of the detection of viral RNA in seminal fluid, suggesting local HIV replication with production of viral particles via the infected sperm cells.

Gantner P, Assoumou L, Leruez-Ville M et al. *HIV-1-RNA in seminal plasma correlates with detection of HIV-1-DNA in semen cells, but not with CMV shedding, among MSM on successful antiretroviral regimens.* J Antimicrob Chemother 2016; 71: 3202 – 3205. doi: 10.1093/jac/dkw271.

Remission after treatment discontinuation in a child treated from birth

Remission after discontinuation of antiretroviral treatment initiated at primary HIV infection was observed in adult post-treatment controllers. For the first time, the cohort ANRS CO10 identified such long-term remission in a child infected perinatally and treated early. Combined antiretroviral therapy was started at 3 months of age and then interrupted by the family between 5.8 and 6.8 years of age. Viral load was undetectable, so treatment was not resumed. Twelve years later, there was still virological remission. The teenager presented immunological characteristics similar to those of adult post-treatment controllers.

Frange P, Faye A, Avettand-Fenoël V et al. *HIV-1 virological remission lasting more than 12 years after interruption of early antiretroviral therapy in a perinatally infected teenager enrolled in the French ANRS EPF-CO10 paediatric cohort: a case report.* Lancet HIV 2016; 3 (1): e49-54. doi: 10.1016/S2352-3018 (15) 00232-5.





Cancer risk in children exposed to didanosine *in utero*

Are children exposed *in utero* to antiretrovirals at greater risk of cancer? By cross-referencing data from an ANRS survey and a pediatric cancer registry, 21 cases of cancers were identified among 15 163 children whose mothers had received antiretrovirals during pregnancy. This total number is not significantly higher than that observed in the general population. Nonetheless, when the treatment included didanosine, the risk was significantly higher, so particular attention should be paid to exposure to this family of drugs during pregnancy.

Hleyhel M, Goujon S, Delteil C et al. Risk of cancer in children exposed to didanosine *in utero*. *AIDS* 2016; 30: 1245-56. doi: 10.1097/QAD.0000000000001051.

In utero exposure to zidovudine is linked to heart anomalies

Antiretroviral therapies administered during pregnancy very effectively prevent mother-to-child HIV transmission. But congenital cardiopathies have been observed in uninfected children exposed to zidovudine. In the framework of the ANRS Enquête Périnatale Française and the trial ANRS 135 PRIMEVA, a link was confirmed between *in utero* exposure to zidovudine and congenital cardiopathies, as well as long-lasting postnatal myocardial remodeling in girls. A potential mechanism, involving mitochondrial dysfunction, should be studied.

Sibiude J, Le Chenadec J, Bonnet D et al. *In utero* exposure to zidovudine and heart anomalies in the ANRS French perinatal cohort and the nested PRIMEVA randomized trial. *Clin Infect Dis* 2015; 61 (2): 270-80. doi: 10.1093/cid/civ260.1.

Prevalence of and risk factors for anal high-risk human papillomavirus infection

Data on the characteristics of and risk factors for anal infection by human papillomavirus (HPV) in HIV-infected women are scarce. The ANRS CO17 ICUBE study in 311 women showed that anal high-risk HPV infection was almost twice as frequent in the anal canal as in the cervix (47.6% and 26.4%, respectively). A CD4+ cell count below 350/ μ L, a cervical lesion, and high-risk HPV infection are factors associated with a high risk of anal infection.

Heard I, Poizot-martin I, Potard V et al. Prevalence of and risk Factors for anal oncogenic human papillomavirus infection among HIV-infected women in France in the combination antiretroviral therapy Era. *J Infect Dis* 2016; 213: 1455 – 61. doi: 10.1093/infdis/jiv751.

Low-dose computed tomography screening for lung cancer in HIV-infected smokers is feasible and effective

In the study ANRS EP48 HIV-CHEST in 14 French centers in HIV-infected smokers with more than 20 pack-years for over 40 years, chest computed tomography showed a significant image that triggered follow-up or diagnosis in 21% of the patients. Only 3.4% of the patients underwent an invasive procedure, without serious adverse drug reactions. Lung cancer was diagnosed in ten patients, and detected by computed tomography in nine of these patients, six at an early and potentially curable stage. Eight of the patients with lung cancer were under 55 years of age. Lung cancer screening could therefore be proposed to people living with HIV at a younger age than is currently the case in the general population.

Makinson A, Eymard-Duvernay S, Raffi F et al. Feasibility and efficacy of early lung cancer diagnosis with chest computed tomography in HIV-infected smokers. *AIDS* 2016; 30: 573 – 81. doi: 10.1097/QAD.0000000000000943.



**Kaposi sarcoma:
lenalidomide is ineffective**

Lenalidomide, an immunomodulator, has proven promising in treatment of HIV-infected patients with Kaposi sarcoma. The ANRS 154 Lenacap trial studied the efficacy and safety of lenalidomide in HIV-positive patients with progressive Kaposi sarcoma despite previous chemotherapy. On the basis of the chosen endpoints, no improvement was noted by the study investigators or by the patients themselves, even though AIDS Clinical Trials Group criteria suggested partial improvement in 40% of patients at week 48.

Pourcher V, Desnoyer A, Assoumou L et al. Phase II trial of lenalidomide in HIV-infected patients with previously treated Kaposi's sarcoma: results of the ANRS 154 Lenacap Trial. AIDS Res Hum Retrov 2016. doi: 10.1089/aid.2016.0069.



**Failure of dual
maraviroc/raltegravir
therapy in a de-escalation
strategy**

The ROCnRAL ANRS 157 trial evaluated a switch from antiretroviral treatment to maraviroc/raltegravir in 44 HIV-1-infected patients with a viral load <50 copies/mL for at least 12 months and with lipohypertrophy. This therapeutic strategy failed to maintain virological suppression. Virological rebound or virological failure was not predicted by the presence of minority resistant variants in the integrase gene or indicating minority X4-tropic viruses, or by ultrasensitive viremia that had not changed during the 24 months of the trial.

Soulié C, Assoumou L, Darty M et al. Virological factors associated with outcome of dual maraviroc/raltegravir therapy (ANRS-157 trial). J Antimicrob Chemother 2015; 70: 3339-44. doi: 10.1093/jac/dkv280.

**HIV: efficacy of three
innovative second-line
combinations in Africa**

The ANRS 12169 2LADY trial in Africa compared three combinations of second-line antiretrovirals in 451 patients who had experienced a first treatment failure: tenofovir/emtricitabine + lopinavir/ritonavir (recommended by the WHO), abacavir + didanosine + lopinavir/ritonavir and tenofovir/emtricitabine + darunavir/ritonavir. The results showed similar and satisfactory virological efficacy of the three combinations (83.2% of patients with a viral load below 200 copies/mL at 48 weeks) and validated the treatment recommended by the WHO.

Ciaffi L, Koulla-Shiro S, Sawadogo A et al. Efficacy and safety of three second-line antiretroviral regimens in HIV-infected patients in Africa. AIDS 2015; 29 (12): 1473-81. doi: 10.1097/QAD.0000000000000709.

**ANRS Temprano has
modified the WHO
guidelines**

The ANRS Temprano trial compared, in seropositive adults with a CD4 cell count above 800/mm³, the benefit of starting antiretroviral treatment either immediately (early treatment) or as a function of WHO criteria (delayed treatment). The participants also received or not preventive treatment of tuberculosis. The results indicate that the risk of severe morbidity was reduced by 44% with early treatment and by 35% with tuberculosis prophylaxis. This shows the benefit of early treatment in resource-limited countries.

Temprano ANRS 12136 Study Group, Danel C, Moh R, Gabillard D et al. A trial of early antiretrovirals and isoniazid preventive therapy in Africa. N Engl J Med 2015; 373 (9): 808-22. doi: 10.1056/NEJMoa1507198.



questions to...

Professor Serge Eholié, Infectious and Tropical Diseases Department, CHU of Treichville, Abidjan, Ivory Coast, main co-investigator of the ANRS Temprano trial.



“MORE SCREENING SHOULD BE ON OFFER IN RESOURCE-LIMITED COUNTRIES”

What were the aims of the ANRS 12136 TEMPRANO trial and what were the main results obtained?

This trial was conducted between March 2008 and January 2015 in nine healthcare centers in Ivory Coast. The aim was to compare delayed initiation of antiretroviral treatment according to World Health Organization (WHO) guidelines ie, as a function of CD4 cell count or of clinical events, with immediate treatment of HIV-seropositive patients. The trial also evaluated the usefulness of six-month chemoprophylaxis of tuberculosis compared with the absence of this preventive treatment. In total, 2056 patients were included and followed up for approximately three years. The results show that immediate treatment reduced by 44% the risk of mortality and morbidity compared with delayed treatment. An additional benefit of chemoprophylaxis, independently of antiretrovirals, was a 35% reduction in severe morbidity, related, in particular, to tuberculosis and to invasive bacterial infections, which are frequent in resource-limited countries. This trial therefore provided scientific proof of the value of treating HIV-infected people as soon as possible and of offering them preventive treatment of tuberculosis.

Following these results, did the WHO guidelines and practices in resource-limited countries change?

The TEMPRANO results, corroborated by the findings of two other large trials – HPTN 05 and START – prompted the WHO to revise its guidelines in June 2015. Since then, in resource-limited countries and in developed countries, it is recommended to start antiretroviral treatment as soon as HIV infection is diagnosed. These guidelines have been progressively adopted by national public authorities. We are now facing what I call operational challenges.

What are these challenges?

The aim today in resource-limited countries is no longer solely to treat people found to be seropositive. We need to go and find them, in other words implement screening of as many people as possible as early as possible. This means we need to increase screening possibilities, which necessitates more financial, material, and human resources. We should also delegate and not leave screening to doctors only. From now on we need a community-based approach to screening. Now we have the scientific evidence, it's up to politicians and funding bodies to put in place the public health strategies needed to maximize antiretroviral therapy coverage.



The impact of the TasP strategy on incidence

In the ANRS TasP study, repeated home-based screening and quick initiation of antiretroviral therapy in mobile clinics in the region of the study (KwaZulu-Natal) had no impact on HIV incidence in this population. These results were presented in an oral communication at the 21st International AIDS Conference, in 2016 in Durban.



Home-based HIV testing: a strategy well accepted in South Africa

The results of the pilot phase of the ANRS TasP trial shows that the repeated offer of screening for HIV and early treatment in the event of seropositivity is well accepted by a rural population in South Africa. In two years, 77% of the targeted population was contacted at home at least once; 80% of women and 75% of men agreed to rapid testing. Among seropositive people aware of their status, 70% had treatment, though only the half of newly diagnosed people sought treatment.

Iwuji CC, Orne-Gliemann J, Larmarange J et al. Uptake of home-based HIV testing, linkage to care, and community attitudes about ART in rural KwaZulu-Natal, South Africa: descriptive results from the first phase of the ANRS 12249 TasP cluster-randomised trial. PLoS Med 2016; 13 (8): e1002107. doi: 10.1371/journal.pmed.1002107.

Immediate treatment of HIV infection: good acceptability

In the framework of the pilot phase of the ANRS TasP trial, analysis of 514 patients who received care in a mobile or government clinic showed that overall acceptability of immediate treatment was high, and four out of five patients started antiretroviral treatment over the first three months of their care. It was patients with the lowest CD4 cell count who started their treatment quickest, as the care teams no doubt prioritized them.

Boyer S, Iwuji C, Gosset A et al. Factors associated with antiretroviral treatment initiation amongst HIV-positive individuals linked to care within a universal test and treat programme: early findings of the ANRS 12249 TasP trial in rural South Africa. AIDS Care 2016; 28 (3): 39-51. doi: 10.1080/09540121.2016.1164808.

Test and treat: voluntary access to care is insufficient

The ANRS TasP trial evaluated whether triple-combination antiretroviral therapy initiated on diagnosis of seropositivity diminishes HIV transmission in the population. In the framework of the pilot phase of the trial, an analysis of 1222 people living with HIV not yet treated indicated that only 37% of them went to a care center in the three months following their screening. This shows the need for innovative intervention strategies to achieve quick access to care for seropositive people.

Plazy M, Farouki KE, Iwuji C et al. Access to HIV care in the context of universal test and treat: challenges within the ANRS 12249 TasP cluster-randomized trial in rural South Africa. J Int AIDS Soc 2016; 19 (1): 20913. doi: 10.7448/IAS.19.1.20913.





Publications



Improving diagnosis and the early treatment of HIV-infected children

The cohort ANRS PEDIACAM in Cameroon shows it is possible in resource-limited countries to provide immediate antiretroviral treatment for HIV-infected infants, because 90% of children included were treated before seven months of age. However, in one-third of cases, the start of the treatment was delayed because of the time needed to make the diagnosis and to put in place antiretroviral treatment. An improvement in pediatric guidelines for the early treatment of HIV infection is therefore needed in resource-limited countries.

*Tejiokem MC, Warszawski J, Ateba Ndongo F et al. Feasibility of routinely offering early combined antiretroviral therapy to HIV-infected infants in a resource-limited country: The ANRS-PediaCAM study in Cameroon. *Pediatr Infect Dis J* 2015; 34 (10): e248-53. doi: 10.1097/INF.0000000000000815.*



Good performance of assays on filter paper for detection of primary infection

Fourth-generation HIV antigen/antibody assays on filter paper effectively detect HIV infection in the primary infection phase. Easy to use, store, and transport, this type of test can be useful when a primary infection is suspected, whereas rapid tests are ill-suited to this situation. The use of such assays could prove particularly valuable in populations that are hard to access or live in remote regions.

*Kania D, Truong TN, Monoya A et al. Performances of fourth generation HIV antigen/antibody assays on filter paper for detection of early HIV infections. *J Clin Virol* 2015; 62/92-7. doi: 10.1016/j.jcv.2014.11.005.*

First reported case of transmission of an HIV-1 M/O recombinant virus

Some cases of recombination of groups O and M HIV-1 have been reported. For the first time, the transmission of such a recombinant virus was observed in a Cameroonian couple in the ANRS RECAMO study. This demonstrates the viability and transmissibility of this recombinant form of HIV-1, and its potential spread within populations.

*Ngoupo PA, Sadeuh-Mba SA, de Oliveira F et al. First evidence of transmission of an HIV-1 M/O intergroup recombinant virus. *AIDS* 2016; 30 (1): 1-8. doi: 10.1097/QAD.0000000000000880.*



Diagnosis of tuberculosis in HIV-infected children: molecular test and alternative sample collection

The diagnosis of tuberculosis is complicated in children by the difficulty of collecting lung samples and the low amounts of bacilli. The ANRS 12229 PAANTHER 01 study in Africa and Asia has demonstrated the efficacy of the Xpert MTB/RIF molecular test using noninvasive collection of specimens (nasopharyngeal aspiration and stools) for the diagnosis of tuberculosis in children living with HIV. Simple, rapid, and of sensitivity equivalent to that of more invasive methods, this combination of Xpert MTB/RIF and alternative specimen collection could facilitate diagnosis in children living with HIV.

*Marcy O, Ung V, Goyet S et al. Performance of Xpert MTB/RIF and alternative specimen collection methods for the diagnosis of tuberculosis in HIV-infected children. *Clin Infect Dis* 2016; 62 (9): 1161-8. doi: 10.1093/cid/ciw036.*



Positive impact of antiretroviral treatment on HSV-2 infection

Prospective, eight-year follow-up of 236 women of the YERELON cohort in Burkina Faso has shown that long-term antiretroviral treatment is associated with decreased cervicovaginal shedding of HSV-2 (herpes simplex virus type 2) in women also infected by HIV. Also observed was a reduction in the number genital ulcerations in these women. This positive effect is maintained over time and is more pronounced when viral suppression is greater.

Low AJ, Nagot N, Weiss HA et al. Herpes simplex virus type-2 cervicovaginal shedding among women living with HIV-1 and receiving antiretroviral therapy in Burkina Faso: an 8-year longitudinal study. J Infect Dis 2016; 213 (5): 731-7. doi: 10.1093/infdis/jiv495.



Spectacular efficacy of direct-acting antivirals on fibrosing cholestatic hepatitis C

Treatment with two direct-acting antivirals, sofosbuvir and daclatasvir, and treatment combining sofosbuvir with a nucleoside analog, ribavirin, resulted in viral eradication in patients with fibrosing cholestatic hepatitis C, a particular recurrence of hepatitis C after liver transplantation the short-term mortality of which is very high. 96% of 23 patients selected from the ANRS CO23 CUPILT cohort presented a sustained virological response twelve weeks after stoppage of treatment. Their clinical condition improved dramatically and they were all alive at the end of the study. Treatment safety was satisfactory and no significant interaction of direct-acting antivirals was observed with the immunosuppressants used to prevent graft rejection.

Leroy V, Dumortier J, Coilly A et al. Efficacy of Sofosbuvir and Daclatasvir in Patients With Fibrosing Cholestatic Hepatitis C After Liver Transplantation. Clin Gastroenterol Hepatol 2015; 13 (11): 1993 – 2001.e2. doi: 10.1016/j.cgh.2015.05.030.



Eradication of the virus reduces the risk of complications in cirrhosis

An ancillary study in 1323 patients with compensated cirrhosis due to chronic HCV infection in the prospective cohort ANRS CO12 CirVir showed that eradication of the virus is associated with a lower risk of serious complications, whether or not related to the liver. Among the 668 patients of these 1323 who showed a sustained virological response during follow-up of 58 months on average, there were fewer cases of hepatocellular carcinoma and hepatic decompensation, and also of bacterial infections and cardiovascular events than in patients with persistent viremia.

Nahon P, Bourcier V, Layese R et al. Eradication of hepatitis C virus infection in patients with cirrhosis reduces risk of liver and non-liver complications. Gastroenterol 2016; 152 (1): 142 – 156.e2. doi: 10.1053/j.gastro.2016.09.009

Bacterial infections, a turning point in compensated cirrhosis

Bacterial infections generally precede a first episode of hepatic decompensation in patients with compensated cirrhosis who are infected by HBV or HCV or both. These infections, which are more frequent in patients carrying HCV than HBV, have a large impact on their prognosis by increasing the short- and long-term risk of death. These results come from an ancillary study of the prospective cohort ANRS CO12 CirVir, which reported 234 cases of bacterial infections in 171 of 1672 patients followed up for an average of 43 months. This study also identified several bacterial infection risk factors: advanced age, lower serum albumin, use of proton pump inhibitors to treat gastric acidity, and absence of virological control.

Nahon P, Lescat M, Layese R et al. Bacterial infection in compensated viral cirrhosis impairs 5-year survival (ANRS CO12 CirVir prospective cohort). Gut 2015; 0:1-12. doi: 10.1136/gutjnl-2015-310275.



Cirrhotic patients: too many adverse drug reactions of the triple-drug therapy with boceprevir

The therapeutic combination of pegylated interferon, ribavirin, and boceprevir is very poorly tolerated in cirrhotic patients with chronic hepatitis C awaiting liver transplantation. This is one of the main findings of the phase 2 pilot study ANRS HC29 BOCEPRETRANSPLANT in 51 patients. Serious adverse drug reactions were observed in 84% of them. The risk of severe infection was particularly high. Three deaths caused by septic shock and complications have been attributed to this treatment. In addition, the low virological efficacy of this triple-drug therapy confirms the value of new treatments without interferon for this type of patient.

Fontaine H, Maynard M, Brouix C et al. Efficacy and safety of boceprevir-based triple therapy in HCV cirrhotic patients awaiting liver transplantation (ANRS HC29 BOCEPRETRANSPLANT). *Clin Res Hepatol Gastroenterol* 2016; doi: 10.1016/j.clinre.2016.06.006.

Direct-acting antivirals have no effect on recurrence of liver cancer

The treatment of hepatitis C by direct-acting antivirals does not raise the risk of recurrence of hepatocellular carcinoma. This is what is suggested by analysis of the findings of 660 patients enrolled in three prospective ANRS cohorts (CO22 HEPATHER, CO12 CirVir and CO23 CUPILT) followed up after curative procedures for liver cancer: radiation ablation, transplantation, or liver resection. The rate of recurrence in these patients treated or not with direct-acting antivirals was comparable in the cohorts HEPATHER and CirVir. (0.7 and 1%, respectively). In the transplanted patients of CUPILT, all treated with direct-acting antivirals, the rate of recurrence was 2.2% after 70 months of follow-up on average. These results contrast with the high rates of recurrence of 8 to 20% reported recently.

Groupe d'étude ANRS sur le carcinome hépatocellulaire. Lack of evidence of an effect of direct-acting antivirals on the recurrence of hepatocellular carcinoma: data from three ANRS cohorts. *Journal of Hepatology* 2016; 65 (4): 734 – 40. doi: 10.1016/j.jhep.2016.05.045.



Benefit of direct-acting antivirals against non-Hodgkin lymphoma

Direct-acting antivirals induce not only a sustained virological response in patients with non-Hodgkin B cell lymphoma associated with chronic HCV infection, but frequently also a hematological response. The highest rate, 73%, was observed among the patients with marginal zone B cell lymphoma, which is strongly associated with HCV. These encouraging findings recorded in 42 patients point to the value of setting up prospective clinical trials on the benefit of direct-acting antivirals in B cell lymphoma associated with HCV. On the other hand, no hematological response was observed in four patients with chronic lymphocytic leukemia, which is not known to be associated with HCV.

Arcaini L, Besson C, Frigeni M et al. Interferon-free antiviral treatment in B-cell lymphoproliferative disorders associated with hepatitis C virus infection. *Blood* 2016; 128 (21): 2527 – 32. doi: 10.1182/blood-2016-05-714667.



Direct-acting antivirals effectively treat hepatitis C recurrence after transplantation

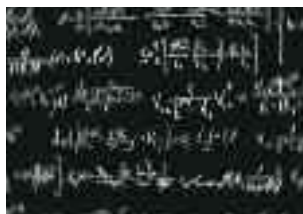
Recurrence of viral hepatitis C after liver transplantation can be treated by a combination of two second-generation direct-acting antivirals: daclatasvir and sofosbuvir. Of 137 liver transplant patients of the ANRS CO23 CUPILT cohort presenting hepatitis C recurrence, 96% were cured after 12 or 24 weeks of treatment, with or without ribavirin, whatever the viral genotype and the stage of liver fibrosis. The rate of serious adverse drug reactions was moderate and there was no clinically important interaction between the direct-acting antivirals and the immunosuppressants used to prevent graft rejection.

Coilly A, Fougereux-Leurent C, de Ledinghen V et al. Multicentre experience using daclatasvir and sofosbuvir to treat hepatitis C recurrence – The ANRS CUPILT study. *J Hepatol* 2016; 65 (4): 711 – 8. doi: 10.1016/j.jhep.2016.05.039.

Dual therapy with daclatasvir and sofosbuvir is effective in HCV genotype 1-mono-infected patients

The combination of the two direct-acting antivirals, daclatasvir and sofosbuvir, is associated with 95% eradication of HCV genotype 1 (HCV-1). This result is based on the analysis of findings in 768 patients of the cohort ANRS CO22 HEPATHER infected by HCV-1 and who have initiated such treatment, with or without the addition of ribavirin, a nucleoside analog. The ideal duration of daclatasvir-sofosbuvir treatment without ribavirin is 12 weeks for patients without cirrhosis and 24 weeks for those with.

Pol S, Bourlière M, Lucier S et al. Safety and efficacy of daclatasvir-sofosbuvir in HCV genotype 1-mono-infected patients. *J Hepatol* 2016; doi: 10.1016/j.jhep.2016.08.021.



The CUPIC algorithm predicts sustained virological response on IFN+RIBA+BOC/TEL

The eradication of HCV by triple-drug therapies based on pegylated interferon and ribavirin, a nucleoside analog, associated with protease inhibitors like boceprevir and telaprevir, can be predicted using the CUPIC algorithm. This algorithm was configured using clinical and laboratory data collected at the outset and at the fourth week of antiviral treatment in 484 patients of the ANRS CO20 CUPIC cohort, and predicted the likelihood that a patient would show a sustained virological response with these triple-drug therapies. This algorithm can, therefore, be used to determine which patients would most benefit from this long-term therapy associated with a major risk of complications. Such information would be particularly useful in countries where new treatments of chronic hepatitis C are as yet unavailable.

Boursier J, Ducancelle A, Vergniol J et al. The CUPIC algorithm: an accurate model for the prediction of sustained viral response under telaprevir or boceprevir triple therapy in cirrhotic patients. *J Viral Hepat* 2015; 22 (12); 1002 – 10. doi: 10.1111/jvh.12433.

The immune system reacts to pegylated interferon

Pegylated interferon alpha-2a as a complement to nucleoside/nucleotide analogs affects the innate and adaptive immunity of patients with chronic HBV infection. 48 weeks of pegylated interferon had an impact on the activation of dendritic cells and natural killer cell functionality in 9 participants of the randomized phase 3 pilot study ANRS HBO6 PEGAN. This treatment also elicits specific T cell responses. Yet no seroconversion of HBV surface antigens was noted up to two years after withdrawal of interferon. This study therefore calls into question the benefit of adding this type of interferon to treatments of chronic hepatitis B.

Bruder Costa J, Dufeu-Duchesne T, Leroy V et al. Pegylated interferon α -2a triggers NK-cell functionality and specific T-cell responses in patients with chronic HBV infection without HBsAg seroconversion. *PLoS ONE* 2016; 11 (6): e0158297. doi: 10.1371/journal.pone.0158297.

Anti-HBV treatments are inadequate in both the developed world and resource-limited countries

Seroclearance of the HBs antigen is a marker of functional cure and hence is the main therapeutic aim in chronic hepatitis B. The ANRS VarBVA study performed in Ivory Coast in HIV/HBV-coinfected patients on antiretroviral treatment including an anti-HBV drug (lamivudine or tenofovir/emtricitabine) shows that the HBs seroclearance rate (6.6%) is similar to that observed in industrialized countries (5-8%). This underscores the need for long-term maintenance of multidrug antiretroviral therapy including an anti-HBV in coinfecting patients in sub-Saharan Africa.

Boyd A, Maylin S, Moh R et al. Hepatitis B surface antigen quantification as a predictor of seroclearance during treatment in HIV-hepatitis B virus coinfecting patients from Sub-Saharan Africa. *J Gastroenterol Hepatol* 2016; 31 (3): 634-44. doi: 10.1111/jgh.13156.



Tenofovir: advantages and limits in coinfecting patients

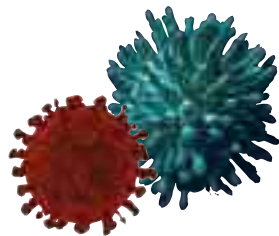
HBV causes chronic and persistent hepatitis because its cccDNA present in the liver escapes current antiviral treatments. Measurement of viral presence in the liver is therefore the most reliable indicator of the degree of infection. Now, even during long-term tenofovir treatment patients coinfecting by HBV and HIV had a residual viral load in the liver, which may be associated with a deficient immune response to HBV and to insufficient viral suppression, allowing maintenance of the pool of cccDNA. This justifies the development of new anti-HBV treatments that target the cycle of viral replication and/or the immune response, so as to hasten elimination of cccDNA.

Boyd A, Lacombe K, Lavocat F et al. Decay of ccc-DNA marks persistence of intrahepatic viral DNA synthesis under tenofovir in HIV-HBV co-infected patients. *J Hepatol* 2016; 65 (4): 683-91. doi: 10.1016/j.jhep.2016.05.014. *Epub* 2016 May 19.

Direct-acting antivirals are well tolerated and effective in HIV/HCV coinfecting cirrhotic patients

HIV/HCV coinfecting cirrhotic patients have long been considered difficult to treat. New direct-acting antivirals studied in the ANRS CO13 HEPAVIH cohort were well tolerated and associated with high virological efficacy in cirrhotic HIV/HCV coinfecting patients. This observation should not, however, lead to less careful monitoring of the liver in these patients.

Sogni P, Gilbert C, Lacombe K et al. All-oral direct-acting antiviral regimens in HIV/hepatitis C virus – coinfecting patients with cirrhosis are efficient and safe: real-life results from the prospective ANRS CO13 – HEPAVIH Cohort. *Clin Infect Dis* 2016; 63 (6): 763-70. doi: 10.1093/cid/ciw379.



Telaprevir worsens anemia caused by ribavirin

The addition of the protease inhibitor telaprevir to dual therapy with pegylated interferon and a nucleoside analog, ribavirin, led to severe anemia in 45% of 67 HIV/HCV coinfecting patients in the phase 2 clinical trial of ANRS HC26 Telaprevir. Although telaprevir induces a sustained virological response in 80% of patients, it also reduces glomerular filtration rate, the volume of liquid filtered by the kidney. As a consequence, ribavirin concentration in the blood increases, thus augmenting its anemic effect. This result therefore underscores the importance of close monitoring of renal function in patients during this type of treatment.

Cotte L, Barrail-Tran A, Vincent C et al. Telaprevir enhances ribavirin-induced anaemia through renal function impairment. *Antiviral Therapy* 2015; 20 (5): 479 – 86. doi: 10.3851/IMP2929.

Intensified vaccination against hepatitis B validated in the case of HIV

In people living with HIV, intensified vaccination against HBV was the most effective short- and long-term regimen among those compared in the phase 3 clinical trial ANRS HB03 HIVVAC-B. It comprises four intramuscular double-dose injections of the vaccine for 24 weeks, and elicits a protective immune response in a higher percentage of patients (71%) than the standard regimen of three intramuscular injections (41%) and than four intradermal injections of low doses of the vaccine (44%). Obtained approximately three years after the first injections, these results confirm the findings recorded four weeks after the last dose.

Launay O, Rosenberg AR, Rey D et al. Long-term immune response to hepatitis B virus vaccination regimens in adults with human immunodeficiency virus 1. *JAMA Internal Med* 2016; 176 (5): 603 – 10. doi: 10.1001/jamainternmed.2016.0741.

Genetic variants of resistance to HCV

Four genetic mutations were for the first time evidenced in three genes coding for coreceptors of the entry of HCV in liver cells (CLDN6, OCLN and SCARB1) by genome sequencing in a case-control study. Mutations in these coreceptors can procure, *in vitro*, resistance HCV infection. These variants, absent from a control group of 121 HIV/HCV coinfecting patients, were identified in only two of 22 patients seropositive for HIV who did not contract hepatitis C despite repeated exposure to the risk of infection. This result suggests that, like HIV, resistance to HCV involves not only the coreceptors but also other complex genetic factors.

Fouquet B, Ghosn J, Quertainmont Y et al. Identification of variants of hepatitis C virus (HCV) entry factors in patients highly exposed to HCV but remaining uninfected: an ANRS case-control study. *PLoS ONE* 2016; 10 (11): e0142698. doi: 10.1371/journal.pone.0142698.



Poor prognosis of liver cancer in HIV/HCV coinfecting patients

The risk of death of patients in presenting hepatocellular carcinoma in a setting of cirrhosis secondary to chronic HCV infection is much higher if they are coinfecting by HIV. Retrospective analysis of imaging data recorded at diagnosis of the hepatocellular carcinoma in such patients participating in two ANRS cohorts (CO13 Hepaviv and HC EP25 Prethevic) show that they are usually affected - 23% of cases - by hepatocellular carcinoma of an infiltrating type associated with portal-obstructing tumors than patients not infected by HIV. Their life expectancy is greatly diminished: a mean of 17 months versus 55 months in the control group.

Lewin M, Gelu-Simeon M, Ostos M et al. Imaging features and prognosis of hepatocellular carcinoma in patients with cirrhosis who are coinfecting with human immunodeficiency virus and hepatitis C virus. *Gastrointestinal Imaging* 2015; 277 (2): 443 - 53. doi: 10.1148/radiol.2015141500.



Boceprevir is effective in relapse of hepatitis C

Addition of a direct-acting antiviral, boceprevir, to dual therapy with pegylated interferon and a nucleoside analog, ribavirin, is an effective way to treat hepatitis C in patients also infected by HIV and in whom this dual therapy has failed. This is what is shown by the ANRS phase 2 clinical trial HC27 BOCEPREVIH in 64 patients. This triple-drug therapy was particularly effective in the 20 patients who experienced relapse of hepatitis C. 90% of them showed a sustained virological response 24 weeks after discontinuation of the new treatment, versus 53% for all patients.

Poizot-Martin I, Bellissant E, Garraffo R et al. Addition of boceprevir to PEG-interferon/ribavirin in HIV/HCV-genotype-1-coinfecting, treatment-experienced patients: efficacy, safety, and pharmacokinetics data from the ANRS HC27 study. *HIV Clinical Trials* 2016; 17 (2): 63 - 71. doi: 10.1080/15284336.2015.1135553.

The effect of pegylated interferon on B cells

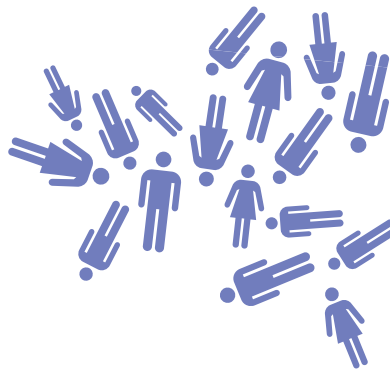
Pegylated interferon alpha-2a as a complement to nucleos(t)ide analogs remodeled B-cell subsets of patients affected by chronic HBV infection. In 48 weeks of treatment, the numbers of plasmablasts and transitional B cells in 9 participants in the randomized phase 3 pilot study ANRS HB06 PEGAN increased compared with those of 14 patients in the control group. Conversely, their populations of naive, natural memory, and low post-germinal center B cells declined compared with the control group. Up to two years after cessation of interferon, no seroconversion of HBV surface antigens was observed. These results therefore question the relevance of this type of interferon in the treatment of chronic hepatitis B.

Aspord C, Bruder Costa J, Jacob MC et al. Remodeling of B-cell subsets in blood during pegylated IFN α -2a therapy in Patients with chronic hepatitis B infection. *PLoS ONE* 2016; 11 (6): e0156200. doi: 10.1371/journal.pone.0156200.

Public health and prevention research



Highlights



Migrants, pre-exposure prophylaxis: two international symposiums

In 2016, the ANRS organized two satellite symposiums at international conferences. The first was on 21 April at AFRAVIH 2016 in Brussels. It was devoted to current policies regarding migrants and their impact on HIV and viral hepatitis infections among migrants from sub-Saharan Africa. The second was on 19 July, during the 21st International AIDS Conference, held in South Africa. It concerned on-demand pre-exposure prophylaxis (PrEP). This conference was the venue for the presentation of the latest results of the last phase of the ANRS IPERGAY the trial which show that on-demand PrEP is effective in preventing the risk of HIV infection in men who have sex with men and who report high-risk behavior.

New PREVAGAY study

In 2009, the PREVAGAY study showed the high incidence of HIV (3.8 for 100 people per year) among men who have sex with men and who frequent gay establishments in Paris. The ANRS decided to renew this survey, this time in five French cities: Lille, Lyon, Montpellier, Nice, and Paris. This field survey done in late 2015 included 2658 men who have sex with men (886 in 2009) and its data on the seroprevalence of HIV, HCV, and HBV, and on practices, are being analyzed.



Is notification of partners possible?

The ANRS launched a study in France to evaluate the notification of partners of people who discover they are HIV seropositive. The notification of partners consists of recently diagnosed people voluntarily identifying and informing their sexual partner(s) or seropositivity and/or drug use, and then urging the partner(s) to go for screening. This research is designed to study the acceptability of notification of partners in the French context, as well as its operational, ethical, and legal feasibility.

Pursue the identification of needs in French Guiana

Guiana is the French department where the HIV epidemic is the most active and widespread. In this context, it is essential to improve understanding and perfect the planning of public health interventions. The ANRS thus launched an epidemiological study of viral hepatitis B, C and D and HIV in populations along the Maroni River, on the border between French Guiana and the Suriname. We lack reliable data on the prevalence of these viruses in these populations, who are isolated, mobile, and vulnerable. Another study supported by the ANRS concerns HIV-infected people who have been in prison one or more times. The purpose is to identify the obstacles to post-prison follow-up of these people.

Public health and prevention research

Strengthening prevention of HCV infection in key populations

The HCV epidemic is very active among drug users and people in prison, which is why the ANRS decided to fund three new studies on this topic. The OUTSIDER project is evaluating the feasibility and efficacy of a proximity prevention program, based on personalized support and education sessions among hard-to-reach intravenous drug users in France. The second study is evaluating the efficacy of injectable buprenorphine in drug users on substitution treatment but who continue to inject opioids. These two studies are being run with support from the patients association AIDES. The PRIDE study is assessing the social acceptability in a prison setting of recommended risk-reduction measures (notably, condoms, opioid substitution therapy, exchange of syringes), given that such measures are still little used in French prisons.



Screening and care in Africa

Two research projects in the social sciences promoted by the ANRS started in 2015 and 2016 in Africa. ANRS12323 DOD-CI was designed to describe the structure of the offer and of the request for screening for HIV and viral hepatitis in Ivory Coast. It also is looking to identify the current obstacles to screening and the conditions needed to move towards universal access to screening. ANRS12354 ENTRAIDE studied access to antiretrovirals, HIV incidence, and the care cascade in Burkina Faso, Ivory Coast, Mali, and Togo.



Social sciences in sub-Saharan Africa and future leads

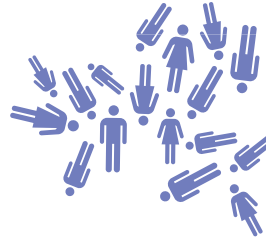
After more than 25 years of social sciences research on HIV/AIDS in sub-Saharan Africa, four ANRS sites in West and Central Africa organized a colloquium to take stock of new understanding, to determine how these disciplines are positioned and renewed in the face of the epidemic, and to propose new lines of thought. Numerous researchers attended this colloquium in Abidjan (Ivory Coast), from 12 to 14 December 2016. The discussions will provide food for thought regarding social sciences research in Africa in the years ahead.

Men who have sex with men in Africa and prevention

Set up in 2015, the ANRS CohMSM cohort will in time determine the most effective preventive measures and the conditions for success in men who have sex with men, a population particularly exposed to HIV. Present in four West African countries, the cohort is very original and has already led to consideration of pre-exposure prophylaxis as a tool for prevention in this population. This study is being conducted under the aegis of the ANRS and Expertise France (in the framework of Initiative 5%).



Publications



These two last years, ANRS work on the prevention of HIV infection and hepatitis has yielded major results that have led to new guidelines and new practices.

On-demand pre-exposure prophylaxis is highly effective

Launched in 2012, the first phase of the ANRS IPERGAY trial has shown that on-demand pre-exposure prophylaxis is effective in preventing the risk of HIV infection, in men who have sex with men and who report high-risk behavior. Compared with a placebo, an antiretroviral combining TDF-FTC (Truvada®) taken at the time of sexual relations reduces by 86% the risk of HIV infection. Subsequently confirmed, these results have in France led to the authorization of pre-exposure prophylaxis and to the reimbursement of its cost.

Molina JM, Capitant C, Spire B et al. *On-demand preexposure prophylaxis in men at high risk for HIV-1 infection*. *N Engl J Med* 2015; 373 (23): 2237-46.
doi: 10.1056/NEJMoa1506273.



Men who have sex with men: increasing prevention

The 2011 survey *Presse Gays et lesbiennes* shows that the frequency of risky sexual practices is still high among male homosexuals. Analysis as a function of serological status indicates that 45% of seropositive men with controlled infection, 55% of seropositive men with uncontrolled infection, 21% of seronegative men, and 34% of men who have not been tested have not adopted any preventive measures. It appears therefore necessary to strengthen preventive measures in this population, in which the prevalence of HIV infection remains particularly high.

Velter A, Saboni L, Sommen C et al. *Sexual and prevention practices in men who have sex with men in the era of combination HIV prevention: results from the Presse Gays et lesbiennes survey, France, 2011*. *Euro Surveill* 2015; 20 (14): pii = 21090.

Drug users: prevention by direct-acting antivirals

In France, close to 60% of injectable drug users are infected by HCV. A modeling study indicates that the possibility of treating injectable drug users with direct-acting antivirals at an early stage of hepatitis C (stage F0 of fibrosis) would clearly reduce the prevalence of infection, by lowering the risk of transmission. Particularly when the measure is accompanied by improved screening and patient management and follow-up. Nevertheless, applied for ten years, generalized access to direct-acting antivirals among injectable drug users does not seem to be a sufficient preventive measure to overcome infection in this population.

Cousin A, Chi Tran V, Deuffic-Burban S et al. *Hepatitis C treatment as prevention of viral transmission and liver-related morbidity in persons who inject drugs*. *Hepatology* 2016; 63 (4): 1090-101.
doi: 10.1002/hep.28227.

Insufficient prevention of HIV and HCV in prisons in Europe

Few European prisons have implemented the measures for prevention of infections recommended notably by the World Health Organization (WHO), such as screening or making condoms available. This is what a five-country (Austria, Belgium, Denmark, France, and Italy) study in prisons has found. Out of a maximum score 9, the mean score of implemented measures ranged between 1.5 and 3.5. So, prisons are a setting where the infectious risk remains particularly high.

Michel L, Lions C, Van Malderen S et al. *Insufficient access to harm reduction measures in prisons in 5 countries (PRIDE Europe): a shared European public health concern.* BMC Public Health 2015; 15: 1093. doi: 10.1186/s12889-015-2421-y.

Methadone treatment and use of cocaine

Whereas management of opioid dependence using methadone substitution treatment reduces occasional cocaine use among drug users, some users continue to use cocaine regularly (6.5% after 12 months of follow-up). These persistent cocaine users present more symptoms of depression and of attention deficit disorder with hyperactivity. Screening for these disorders is therefore crucial, given that cocaine decreases the efficacy of methadone treatment and increases the risk of overdose.

Roux P, Lions C, Vilotitch A et al. *Correlates of cocaine use during methadone treatment: implications for screening and clinical management (ANRS Methaville study).* Harm Reduct J 2016; 13:12. doi: 10.1186/s12954-016-0100-7.



Utility of personalized support in drug users

Educational sessions delivered notably by peers to intravenous drug users significantly reduce practices associated with the risk of HIV and HCV transmission. ANRS-AERLI found that this community-based intervention was also associated with a decrease in complications at the injection site and with increased access to HCV screening. Transportable and inexpensive, this risk reduction strategy is therefore useful for difficult-to-reach people in the healthcare system.

Roux P, Le Gall JM, Debrus M et al. *Innovative community-based educational face-to-face intervention to reduce HIV, hepatitis C virus and other blood-borne infectious risks in difficult-to-reach people who inject drugs: results from the ANRS-AERLI intervention study.* Addiction 2016; 111 (1): 94-106. doi: 10.1111/add.13089.

Roux P, Rojas Castro D, Ndiaye K et al. *Increased uptake of HCV testing through a community-based educational intervention in difficult-to-reach people who inject drugs: results from the ANRS-AERLI study.* PLoS One. 2016; 11 (6): e0157062.

HIV self-testing: more than 250 guidelines

HIV self-testing has been available in France since 2015. Before its marketing, 72 experts on screening in the general population and the most exposed populations produced good practice guidelines. In all, 263 guidelines were produced to go with proper use of self-testing, according to the needs and preferences of potential users in each group. The quality of the information concerning the use of the test and access to care, should the result be positive, were among the main concerns. These guidelines were forwarded to the public authorities to expedite access to this new method of screening.

Greacen T, Kersaudy-Rahib D, Le Gall JM et al. *Comparing the information and support needs of different population groups in preparation for 2015 government approval for HIV self-testing in France.* Plos One 2016; 11 (3): e015256. doi: 10.1371/journal.pone.0152567.



**Bruno Spire,
Research Director
at Inserm and
co-president
of ANRS coordinated
action no. 18**



questions to...

“ASSESSING NEW PREVENTION TOOLS AT THE POPULATION LEVEL”

What are currently the main questions in research in prevention?

The main question, from which all others derive, is to know how, today, it is possible to have an impact on the epidemic with the new tools of pre-exposure prophylaxis (PrEP) and treatment as prevention (TasP), which are now known to be effective on an individual scale. The epidemic affects different populations each of which has potential drivers of and barriers to specific access. The aim then is to set up research to determine how these new tools can be functional collectively and stop the HIV epidemic.

What research is ongoing or planned in this regard?

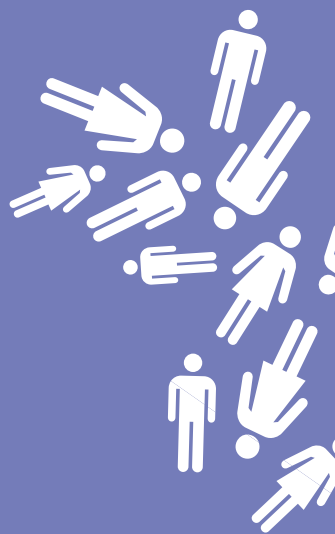
Screening is the gateway to these tools. So, the ANRS projects essentially aim to improve screening and access to PrEP in the most exposed populations. One line of work relates to self-testing, which can meet screening needs for people who don't consider themselves as part of classic at-risk groups, but who nonetheless are concerned by risky practices. Research is underway to identify these people, how they access self-testing, and their outcome. We are also thinking about the notification of partners, in which the sexual partners of people recently diagnosed as seropositive are informed of their possible exposure to HIV, with a view to encouraging them to seek HIV testing. This type of approach has proven effective in several countries. This enables the identification of many seropositive people unaware of their status and breaks the chains of infection. So, we are exploring different ways of notification that would be acceptable to people in France, while remaining ethical.

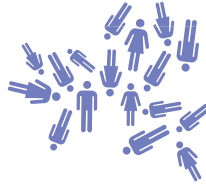
Furthermore, we are involved in Prévenir, a vast project within the framework of Towards Paris without AIDS and Paris-Île-de-France region without AIDS. The aim is to set up PrEP on a large scale and to show that a prevention strategy based on screening and PrEP limits the spread of HIV among the most exposed people. This study is under way in the Paris-Île-de-France region and will involve at least 3000 people, who will be followed up for three years. It will also compare two types of support of participants: community-based, done by members of the nonprofit organization AIDES, or by healthcare personnel based on the model of therapeutic education.

Lastly, we have research projects targeting migrants, such as planned research to determine whether motivational interviews encourage migrants to accept and make use of PrEP. Thus, we specifically target operational research at different exposed populations to determine how to get them to adopt new prevention tools. I would add that we are striving to do the same in resource-limited countries. Several studies, directly inspired by our projects in the developed world, are underway in key populations in countries of sub-Saharan Africa.

What role do patient organizations play in these studies?

Their role is increasingly important. I think we can say that community research is now at the heart of the ANRS prevention research. Clearly, it is easier to conduct this research by involving the people concerned, rather than doing the work in a purely academic sense. This greatly facilitates access in the field and the adaptation of research tools. In parallel, representatives of patients train themselves in research issues and become full-blown researchers. AIDES, for example, is a co-investigator of the Prévenir study. The participation of associations therefore constitutes a permanent and mutual enrichment of the value of research.





Towards targeted screening in emergency departments?

In France, between 15 000 and 30 000 people are unaware they are HIV seropositive. To identify and treat them, generalized screening with rapid HIV testing was first envisaged. Targeted screening could be more appropriate, since it appeared that most of the people concerned belong to the groups most exposed to infection. This new strategy was evaluated in eight emergency departments in the Paris-Île-de-France region. All patients admitted were invited to complete a questionnaire, which covered notably country of birth and sexual orientation. A nurse offers rapid HIV testing to those people identified as being at risk. The study also sought to define the role of nurses in this screening.

Leblanc J, Rousseau A, Hejblum G et al. *The impact of nurse-driven targeted HIV screening in 8 emergency departments: study protocol for the DICI-VIH cluster-randomized two-period crossover trial.* BMC Infect Dis 2016; 16:51. doi: 10.1186/s12879-016-1377-6



Sub-Saharan migrants: close to 50% of infections occur in France

In France, one-quarter of cases of HIV/AIDS concern migrants from sub-Saharan Africa. The ANRS PARCOURS study indicated that 35 to 49% of them were infected by HIV after their arrival in France. Conducted in the Paris-Île-de-France region, the study related to a representative sample of 898 seropositive patients from sub-Saharan Africa who had been living in France for a median of 12 years. The estimation was based on a combination of life-event information and modeling of the decrease in CD4+ T cell count. It shows the need in this population for a specific prevention and risk reduction strategy, in addition to screening and treatment.

Desgrées-du-Loû A, Pannetier J, Ravalihasy A et al. *Sub-Saharan African migrants living with HIV acquired after migration, France, ANRS PARCOURS study, 2012 to 2013.* Eurosurveillance 2015; 20 (46): pii = 30065. doi: <http://dx.doi.org/10.2807/1560-7917.ES.2015.20.46.30065>

Sub-Saharan migrants: hardship and risk

In migrants from sub-Saharan Africa living in France, hardship increases the risk of HIV infection. This was shown by the ANRS PARCOURS study, which was based on a survey among 2468 migrants, 926 of whom were HIV seropositive and 779 had chronic hepatitis B. More than 40% of people questioned had lived for at least one year without a residence permit and 20% without stable accommodation. These are situations that favor occasional or concomitant sexual relations, which, moreover, were more frequently reported by people infected by HIV. So, hardship in this population appears to be an indirect determinant of HIV infection.

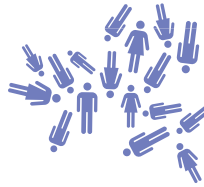
Desgrées-du-Loû A, Pannetier J, Ravalihasy A et al. *Is hardship during migration a determinant of HIV infection? Results from the ANRS PARCOURS study of sub-Saharan African migrants in France.* AIDS 2016; 30 (4): 645-56. doi: 10.1097/QAD.0000000000000957

Increasing unemployment among people living with HIV

Between 2003 and 2011, the percentage unemployment among people infected by HIV rose from 12.6% to 15.8%, a relative increase of 25%, versus 8% in the general population. This is the finding of the ANRS VESPA surveys among some 3000 patients followed up in hospital. After taking into account sociodemographic differences, the difference from the general population persists and is even accentuated. In addition, compared with 2003, seropositive patients had more difficulty finding work in 2011, after diagnosis. These results show that, despite improved treatments and care, people infected by HIV always have more difficulty finding a job.

Annequin M, Lert F, Spire L et al. *Has the employment status of people living with HIV changed since the early 2000s? Aids 2015; 29: 1537-47. doi: 10.1097/QAD.000000000000000722.*





Erroneous estimates of HIV incidence

In 2014 and 2016, the Global Burden of Disease published estimates of the incidence of HIV by country. European, notably French, researchers showed that these incidences were underestimated and unrealistic, because they were based solely on mortality data. In rich countries at least, antiretrovirals have considerably modified the natural history of infection. The mortality associated with AIDS alone does not account for the number of new infections. HIV monitoring systems, such as those in France, readily show this.

Supervie V, Archibald CP, Costagliola D et al. *GBD 2013 and HIV incidence in high income countries*. *Lancet* 2015; 385 (9974): 1177. doi: 10.1016/S0140-6736 (15) 60626-2.

Supervie V, Costagliola D. *Time for a revolution in tracking the HIV epidemic*. *Lancet HIV* 2016; 3 (8): e337-9. doi: 10.1016/S2352-3018 (16) 30089-3.

Generational approach to sexual practices among men who have sex with men

A longitudinal analysis of the French Gay Press surveys of 1985 to 2011 shows an increase in sexual practices common to each generation of men who have sex with men. Renewed sexual involvement since the mid-1990s thus concerns older and younger generations alike. Adaptation of practices in response to the HIV epidemic thus seems more influenced by the context of the present than by the experience of each generation.

Méthy N, Velter A, Semaille C, Bajos N. *Sexual behaviours of homosexual and bisexual men in France: a generational approach*. *PLoS One* 2015; 10 (3): e0123151. doi: 10.1371/journal.pone.0123151.

The reality of the risk of HIV transmission during antiretroviral therapy

The risk of HIV transmission with a viral load well controlled by antiretrovirals is low, but is it zero? A review of studies done in serodifferent couples shows that at most one case of transmission occurred. The authors consider that the risk of transmission is below an estimated threshold of between 5 and 8 cases for 100 000 sexual acts in heterosexual couples. They remark that current findings are insufficient to estimate this risk in homosexual couples.

Supervie V, Viard JP, Costagliola D, Breban R. *Risk of HIV transmission under combined antiretroviral therapy: toward risk zero?* *J Acquir Immune Defic Syndr* 2015; 68 (3): e41-2. doi: 10.1097/QAI.0000000000000471.

The underpinnings of adherence in seropositive adolescents in Brazil

A team supported by the ANRS followed up longitudinally for one year a cohort of 268 Brazilian teenagers infected by HIV perinatally and on antiretrovirals, so as to determine what underpinned their adherence to treatment. Approximately one-third of the teenagers were not adherent. The two factors associated with good adherence were the feeling of personal efficacy in taking the treatment and a low number of adverse drug reactions. This study thus highlights the need to improve adherence in Brazilian teenagers and points out possible means of intervention.

Côté J, Delmas P, de Menezes Succi RC et al. *Predictors and Evolution of Antiretroviral Therapy Adherence Among Perinatally HIV-Infected Adolescents in Brazil*. *J Adolesc Health*. 2016. 59 (3): 305-10. doi: 10.1016/j.jadohealth.2016.05.004.



The preventive effect of early antiretroviral treatment is unlikely to offset an increase in risky behavior

The ANRS 12136 TEMPRANO trial in Ivory Coast showed the benefit of early antiretroviral treatment and confirmed its preventive effect on the risk of transmission of HIV to sexual partners. Also investigated was whether this preventive effect was offset by increased risky sexual behavior of patients. Modeling indicates that very large, and hence unlikely, changes in risky behavior would be necessary to offset the decrease in the risk of HIV transmission. The authors consider that scale-up of early treatment should lead to a reduction in HIV transmission, even against a backdrop of increased risk behavior.

Jean K, Boily MC, Danel C et al. *What level of risk compensation would offset the preventive effect of early antiretroviral therapy? Simulations from the TEMPRANO trial*. *Am J Epidemiol*. 2016.

Coinfected men who have sex with men: persistent risks

The advent of new therapies against HCV offers the possibility of controlling the infection. This calls for identification of the risk factors of HCV infection/transmission in the most exposed populations. The survey ANRS VESPA2 showed persistence of factors and behavior associated with the risk of HCV infection in men who have sex with men who have been treated for and cured of HCV: sexually transmitted infections, participation in sex parties, nonsystematic use of condoms, fist fucking, use of drugs during sex. Whence the need to adapt prevention messages accompanying anti-HCV treatments.

Marcellin F, Demoulin B, Suzan-Monti M et al. Risk factors for HCV reinfection or transmission in HIV-HCV coinfecting MSM (ANRS-VESPA2 French national survey). *JAIDS* 2015; 70 (5): e179-82. doi: 10.1097/QAI.0000000000000836.



Cannabis and insulin resistance in HIV/HCV-infected patients

Among 703 patients carrying HIV and HCV and followed up in the ANRS HEPAVIH CO-13 cohort, 45% reported use of cannabis in the six months before the first visit. Follow-up shows that the participants who used cannabis had a risk of insulin resistance reduced by 60%, compared with those who did not use cannabis. Already observed in the general population in cross-sectional studies, this preventive effect of cannabis is particularly interesting as coinfecting patients have a heightened risk of developing insulin resistance or diabetes. Clinical trials should be envisaged to evaluate the benefit in the HIV/HCV-infected patients of cannabis in a pharmaceutical formulation.

Carrieri P, Serfaty L, Vilotitch A et al. Cannabis use and reduced risk of insulin resistance in HIV-HCV infected patients: a longitudinal analysis (ANRS CO13 HEPAVIH). *Clin Infect Dis* 2015; 61 (1): 40 – 8. doi: 10.1093/cid/civ217.

Is the end of the HIV epidemic among drug users in Vietnam possible?

Results from the ANRS DRIVE-IN cohort, in collaboration with the American National Institute of Drug Abuse, at Hai Phong, indicate that it is possible to end the HIV epidemic among injectable drug users. In this cohort, the prevalence of HIV is 25% (5% among new injectors). In 2006 and 2009, the prevalence was 66% and 48%, respectively. A decline in the epidemic is thus clearly observed in this population. Increased screening and treatment of seropositive users are, however, necessary to accelerate this decline, given that at the same time the HCV epidemic remains particularly active.

Des Jarlais DC, Thi Huong D, Thi Hai Oanh K et al. Prospects for ending the HIV epidemic among persons who inject drugs in Haiphong, Vietnam. *Int J Drug Policy* 2016; 32: 50-6. doi: 10.1016/j.drugpo.2016.02.021.



Injectable drug users in Senegal: a better understood population

The ANRS UDSEN survey has defined the situation of injectable drug users in the region of Dakar. This mostly male population is socially vulnerable and outside the healthcare system. HIV (5.2%) and HCV (23.3%) prevalences are 7- and 40-fold higher than in the general population. These results have led to the opening, in the Fann University Hospital in Dakar, of the CEPIAD, the first center in West Africa devoted to addictions, including a methadone program.

Leprêtre A, Ba I, Lacombe K et al. Prevalence and behavioural risks for HIV and HCV infections in a population of drug users of Dakar, Senegal: the ANRS 12243 UDSEN study. *J Int AIDS Soc* 2015; 18: 19888. doi: 10.7448/IAS.18.1.19888.

Vaccine research



Highlights



The ANRS and the University Paris-Est Créteil set up the Vaccine Research Institute to expedite the development of vaccines against HIV/AIDS.

End of preclinical studies

The Vaccine Research Institute (VRI) has completed three preclinical studies of different candidate vaccines in non-human primates, two on a preventive vaccine, and one on a therapeutic vaccine. The results show that the strategy targeting dendritic cells shows good safety and induces good immunogenicity, both cellular and humoral. These studies have also permitted selection of monoclonal antibodies, adjuvant, and prime-boost vaccine associated with a better immune response for each of the two vaccine approaches.



Selection of two candidate vaccines

Following the preclinical results, the VRI selected better candidate vaccines for their development and production. The vaccines selected are based on a recombinant anti-CD40 antibody, which was humanized and fused with HIV-1 antigens. The vaccines are intended to target and activate dendritic cells. Depending on the nature of the HIV-1 antigens used, the candidate vaccines are intended for preventive or therapeutic trials of HIV infection.

Partnership for the production of candidate vaccines

In November 2016, the VRI and the ANRS signed a partnership agreement with the bioproduction service provider Novasep, allied with GTP Technology. This agreement relates to the production of two candidate vaccines selected by the VRI. These will be produced in 2017-2018 under conditions in line with good manufacturing practices. The launch of phase 1/2 clinical trials (VRI06 and VRI07) evaluating these two candidate vaccines in humans, in a preventive and therapeutic approach, is scheduled for 2019.

Launch of a European alliance

On the initiative of Professor Yves Lévy and Professor Giuseppe Pantaleo, the European HIV Vaccine Alliance (EHVA) was launched in January 2016. Coordinated by Professor Lévy, EHVA has 39 partners in 15 countries. Its aim is to develop a multidisciplinary vaccine platform to evaluate new candidate preventive and therapeutic anti-HIV vaccines. It receives European funding to the tune of €22 million, plus €6 million from the Swiss government.



Overall evaluation

The VRI has the label Laboratory of Excellence (Labex) within the framework of the investments in the future program (PIA1). This label, awarded for ten years, involves a review at the halfway mark. Overseen by the ANR, an international jury assessed the VRI in June 2015, using criteria concerning science, governance, organization, research advances, and valorization. The jury very favorably reviewed the VRI, which should therefore be renewed for a longer period.



Publications



The Vaccine Research Institute's scientific output for 2015-2016 bears witness to the diversity and quality of its research teams.

The inflammasome, the origin of the innate and adaptive response

The inflammasome is activated in response to a variety of pathogens, and thus plays an essential role in the innate and adaptive immune responses. *In vivo* injection of MVA HIV-B (recombinant modified vaccinia Ankara virus encoding HIV antigens) activates the inflammasome in subcapsular macrophages of the lymph nodes, and this is immediately followed by death of the cells, which release ASC specks, extending the effect of the immune reaction. This generates an influx of inflammatory cells and mobilizes T cells from the circulation, thus increasing the magnitude of the T cell response. This is of interest in developing vaccine strategies to activate the inflammasome pathway.

Sagoo P, Garcia Z, Breart B et al. *In vivo imaging of inflammasome activation reveals a subcapsular macrophage burst response that mobilizes innate and adaptive immunity.* Nat Med 2016; 22 (1): 64-71. doi: 10.1038/nm.4016.



Mass cytometry reveals the impact of vaccination on the proportions of different B cell subsets

Vaccine evaluation will be improved if we can broaden our understanding of the abundance and phenotype of B cell subsets that are induced or perturbed by exogenous antigens. A mass cytometry study in cynomolgus macaques has described in detail B cell subsets in the blood before vaccination, then 1 week and 1 month after two injections of an MVA-HIV-B (recombinant modified vaccinia Ankara virus encoding HIV antigens) vaccine. This study has revealed the diversity and phenotypic complexity of B cells. It has also identified the B cell subsets whose proportions are significantly altered by vaccination and which correlate in frequency with the intensity of the antibody response to the vaccine.

Pejoski D, Tchitchek N, Rodriguez Pozo A et al. *Identification of vaccine-altered circulating B cell phenotypes using mass cytometry and a two-step clustering analysis.* J Immunol 2016; 196: 4814-31. doi: 10.4049/jimmunol.1502005.

T cells respond to a vaccine combining HIV-Lipo-5 and rMVA-HIV

A study was done of the immunogenicity in cynomolgus macaques of different vaccine strategies combining lipopeptides (HIV-Lipo-5) and MVA-HIV-B (recombinant modified vaccinia Ankara virus encoding HIV antigens), used as a vector of vaccine antigens, both of which can trigger T cell responses to HIV. The most effective induction of a response by T cells requires first stimulation by HIV-Lipo-5 and then injection of MVA-HIV-B. This chronology could be used in future prophylactic approaches to HIV.

Dereuddre-Bosquet N, Baron ML, Contreras V et al. *HIV specific responses induced in nonhuman primates with ANRS HIV-Lipo-5 vaccine combined with rMVA-HIV prime or boost immunizations.* Vaccine 2015; 33; 2354-9. doi: 10.1016/j.vaccine.2015.03.032.

Delivering HIV Gagp24 to dendritic cells induces a strong humoral response

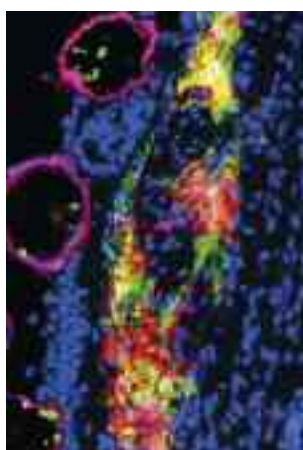
Targeting the endocytic receptors of dendritic cells, like DCIR, using monoclonal antibodies fused to specific antigens, is a vaccine approach developed to enhance the low immunogenicity of protein-based vaccines. Researchers at the Vaccine Research Institute (LabEx VRI) have made humanized recombinant anti-DCIR antibodies able to cross-react with the receptor of the macaque cynomolgus, and have fused them with HIV Gagp24 protein. *In vivo* administration of this construct induced a strong humoral response via the production of anti-Gag antibodies, thus revealing the value of developing more vaccines that target dendritic cell receptors, such as DCIR.

Flamar AL, Contreras V, Zurawski S et al. *Delivering HIV Gagp24 to DCIR induces strong antibody responses in vivo*. PLoS ONE 2015; (9): e0135513. doi: 10.1371/journal.pone.0135513.

In vivo tracking of Langerhans cells targeted by a vaccine

A fusion protein, composed of HIV antigens and of monoclonal antibody targeting Langerin, a receptor of epidermal Langerhans cells, was used to track *in vivo* the cells targeted by this vaccine in non-human primates. Rapid changes in the network of Langerhans cells were observed, including their activation and migration outside the epidermis. Vaccination targeting these cells improves the anti-HIV immune response. Although co-injection of resiquimod, a ligand that modulates the immune response, did not significantly improve the antibody response, it did, however, stimulate the recruitment of HLA-DR+ inflammatory cells.

Salabert N, Todorova B, Martinon F et al. *Intradermal injection of an anti-Langerin-HIVGag fusion vaccine targets epidermal Langerhans cells in nonhuman primates and can be tracked in vivo*. Eur. J. Immunol 2016; 46: 689-700. doi: 10.1002/eji.201545465.



A vaccine targeting LOX-1 induces anti-HIV immune responses in Rhesus macaques

To use vaccines to induce protective immunity against HIV-1, it is necessary to increase the antigenicity of the HIV-1 envelope protein. To do this, the protein of the HIV-1 envelope gp140 was fused with a recombinant humanized antibody against LOX-1, a receptor expressed by dendritic cells, so as to target the HIV-1 antigens specifically on dendritic cells presenting LOX-1. The first tests in non-human primates showed that this vaccine strategy of targeting dendritic cells induced strong cellular and humoral responses when used to prime the immune process and to boost it. These results show that this vaccine approach targeting dendritic cells should be pursued further.

Zurawski G, Flamar AL, Richert L et al. *Targeting HIV-1 Env gp140 to LOX-1 Elicits Immune Responses in Rhesus Macaques*. PLoS ONE 2016; 11 (4): e0153484. doi: 10.1371/journal.pone.0153484.

Time-course gene set analysis to monitor the dynamics of gene expression during a vaccine trial

Genomic analyses of groups of predefined genes can include time as a parameter, in time-course gene set analysis or TcGSA, which can be used to track genes whose expression varies over time. Applied to the vaccine trial DALIA-1, TcGSA revealed, at vaccination, significant changes over time of 69 groups of genes. While more conventional methods of analyzing gene expression have failed to demonstrate these time-dependent changes, TcGSA seems to be a tool of choice for analyzing the dynamics of gene expression.

Hejblum BP, Stinner J, Thiebaut R et al. *Time-course gene set analysis for longitudinal gene expression data, gene expression data*. PLoS Comput Biol 2015; 11 (6): e1004310. doi: 10.1371/journal.pcbi.1004310.



Variants in partial least squares approaches applied in a genomics context

The combination of two blocks of genomic data generates difficulties in bioinformatic processing, because of their size and complexity. This study examined the performance of the partial least square (PLS) method, so as to study the link between two large data sets while simultaneously selecting the most contributory variables. Two extensions of PLS, gPLS (group PLS) and sgPLS (sparse group PLS), were used to study the relation between two different types of genomics findings (eg, single nucleotide polymorphism and gene expression) or between genomics data and multivariate phenotypes. This work shows that these tools can be used to study the relation between the abundance of genes and the immunological response to a vaccine.

Liquet B, Micheaux PL, Hejblum BP et al. *Group and sparse group partial least square approaches applied in genomics context*. *Bioinformatics* 2016; 32 (1); 35-42. doi: 10.1093/bioinformatics/btv535.

Repeated cycles of recombinant human interleukin 7 restore CD4 T cell levels

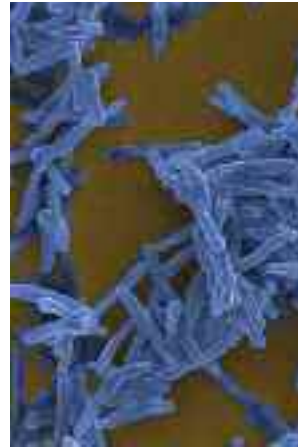
Phase 1 and 2 trials in HIV-infected patients have shown that immunotherapy based on a three-week cycle of subcutaneous injections of recombinant human interleukin 7 (r-hIL-7) is well tolerated and improves reconstitution of CD4 T cells. In the phase 2 trials INSPIRE-2 and INSPIRE-3, it was shown that repeated cycles of r-hIL-7 were well tolerated by the 107 patients concerned and, in most of them, restored the CD4 T cell count to above 500/mL.

Thiébaud R, Jarne A, Routy JP et al. *Repeated cycles of recombinant human interleukin 7 in HIV-infected patients with low CD4 T-cell reconstitution on antiretroviral therapy: results of 2 phase II multicenter studies*. *Clin Infect Dis* 2016;62. doi: 10.1093/cid/ciw065.

Microbiome and HIV infection, a subject yet to be explored

What happens in the intestinal microbiome, which interacts with immune mechanisms, at HIV infection? A review of relevant studies revealed various manifestations, such as changes in microbial diversity depending on serological status, deleterious effects in populations according to the people infected, or the influence of triple-drug therapies on restoration of the microbiome. Better understanding of the mechanisms involved, notably of the influence of microorganisms on viral replication, would enable us to propose therapeutic adjuvants to help control disease development through the microbiome

Dubourg G, Surenaud M, Lévy Y et al. *Microbiome of HIV-infected people*. *Microb. Pathog* 2016; pii: S0882-4010 (16) 30045-6. doi: 10.1016/j.micpath.2016.05.015.



Vaccine research: recent developments in clinical trials

Despite the large number of candidate vaccines, the selection of a vaccine strategy against HIV remains a challenge in terms of assessing its clinical efficacy. Despite recent efforts, the transition from phase 2 immunogenicity trials to phase 2b efficacy trials is always a critical point. The criteria for deciding this passage should take into account a large spectrum of immunogenicity variables. The development of statistical methods to manage these variables therefore seems essential in decision-making in the development of HIV vaccines.

Richert L, Lhomme E, Fagard C et al. *Recent developments in clinical trial designs for HIV vaccine research*. *Hum Vac Immuno* 2015; 11 (4): 1022-29. doi: 10.1080/21645515.2015.1011974.

Early initiation of combined antiretroviral therapy preserves immune function in the gut

HIV infection results in profound depletion of CD4+ T cells in the intestinal mucosa. The resulting alteration of the intestinal barrier allows the passage of microbial products (microbial translocation) into the blood, leading to activation of new targets for the virus, and, in the end, disease progression. Analysis of gene expression in patients who started antiretroviral therapy soon after infection shows that the intestinal lymphatics are preserved and/or restored, thus limiting microbial translocation. These findings provide an additional argument for early initiation of treatment in HIV-infected people.

Kök A, Hocqueloux L, Hocini H et al. *Early initiation of combined antiretroviral therapy preserves immune function in the gut of HIV-infected patients*. *Mucosal Immunol* 2015; 8: 127-40. doi: 10.1038/mi.2014.50.

Valorization and transfer



Transmission, communication

Exchanges with the scientific community, institutional partners of the ANRS, and the media have put the spotlight on the latest scientific advances. Entrusted by the International AIDS Society with organizing the 9th IAS Conference on HIV Science, the ANRS has mobilized research teams and its partners for this event, which will take place in Paris in July 2017.



A special issue of *The Lancet* on France

In its 2 May 2016, special issue entitled "France: nation and world," *The Lancet* reviewed the contribution of the French healthcare system to the advent of universal health coverage and the role of France in health diplomacy. The director of the ANRS, Professor Delfraissy, contributed two articles to this special issue, one of which presented REACTing, a new concept for scientific coordination and fundraising to improve preparedness during health crises, notably infectious, set up under the aegis of Inserm.

Updating guidelines

Under the aegis of the ANRS and the CNS (French National AIDS & Viral Hepatitis Council), guidelines for the medical management of people living with HIV and of people infected by hepatitis C virus were updated.

Concerning HIV infection, in 2015 the group headed by Professor Philippe Morlat (CHU de Bordeaux) updated three chapters of previous guidelines (dating from 2013), devoted to the optimization of antiretroviral treatment when there is viral suppression, the treatment of children and teenagers, and the wish to have children and for pregnancy (including management of infants born to mothers living with HIV). This same group at the same time drew up guidelines on pre-exposure prophylaxis (PrEP). In 2016, several other chapters were updated, notably those concerning the initiation of a first antiretroviral treatment, the management of virologic failure in adults, resistance to antiretrovirals, and primary infection.

At the request of the Minister of Health and Social Affairs, who announced in May 2016 universal access to treatment of hepatitis C, the ANRS and CNS entrusted Professor Daniel Dhumeaux with the responsibility of updating the report on the therapeutic management and follow-up of all people infected by the hepatitis C virus. Presented to the minister in October 2016, the updated report contained guidelines to ensure that the most vulnerable or those outside the healthcare system could be tested and receive treatment of their hepatitis C.

PARIS 2017: UNITED AGAINST HIV

Two major events will take place in Paris in 2017:

- the launch of City Hall (Mairie de Paris) program Towards Paris without AIDS, initiated within the framework of the world's great cities committed to end the epidemic and with which the ANRS is associated through its research project PREVENIR.

- the 9th IAS Conference on HIV Science, organized jointly by the International AIDS Society and the ANRS in Paris.

A particular effort was made to integrate basic research, and this led to increased representation of researchers at the conference.

In the framework of the HIV Cure program, a symposium will be held at the Institut Curie in partnership with French and overseas oncology teams. The ANRS has organized a series of actions to mobilize the scientific, nonprofit, and institutional communities. The aim is to bring together all stakeholders involved in the global response to HIV and to raise public awareness. A program of grants for young researchers was put in place. Different communication tools were developed and awareness-raising events are scheduled.



Two ANRS sites in the spotlight

The PAC-CI program of the ANRS site in Ivory Coast celebrated its 20th anniversary on the occasion of its scientific meeting of 16 and 17 March 2015. Through its partnership with research and teaching institutions in Bordeaux, this program has trained numerous researchers and conducted much research on HIV. Certain trials were determinant in the drawing up of World Health Organization guidelines and for the improvement of universal treatment of patients. Furthermore, the ANRS site in Cameroon celebrated its ten years of official existence in January 2016. Seventy-five research projects were funded by the ANRS there during this period, on prevention, treatment, and the origin of HIV.

Vietnam and Senegal: the ANRS to the fore

The scientific boards of the ANRS sites in Vietnam and Senegal met, respectively, in November 2015 and 2016, during scientific meetings on the national fight against AIDS in these two countries. This underscores the role of the ANRS in these programs and alongside the national authorities. It also shows how the two sites are increasingly integrated in the university network of these countries, which has been one of the aims of the ANRS.

A NEW PRESIDENT FOR AC12

In November 2015, Professor Pierre-Marie Girard replaced Professor François Dabis as president of ANRS coordinated action 12 on research in resource-limited countries. Head of the Infectious and Tropical Diseases Department at the Saint-Antoine Hospital in Paris, Professor Girard has long been involved in the activities of the ANRS. He was, notably, one of the two coordinators of the ANRS site in Senegal until 2014.

THREE NEW WORKING GROUPS

Three new working groups were created in AC12 on research subjects deemed to be priorities. The first group is working on viral hepatitis, notably hepatitis B, and in particular mother-to-child HBV transmission, new diagnostic tools, and the search for algorithms for treatment decision-making in resource-limited settings. The second working group focuses on key populations, notably in terms of implementation of pre-exposure prophylaxis among men who have sex with men and among sex workers in resource-limited countries. The third and last working group is studying innovative strategies for the management of HIV-infected patients in these countries, with regard to antiretroviral treatments and follow-up modalities.

The contribution of the scientific committee

The role of the ANRS scientific committee is crucial in terms of the broad scientific aims of the agency. Presided over by Professor Françoise Barré-Sinoussi, and by Professor Stefano Vella, this committee comprises leading, internationally recognized scientists, who collectively provide specialist expertise. They meet once a year and on each occasion the ANRS presents a cross-cutting theme covering the developed world and resource-limited settings, HIV/hepatitis, and the participation of all research disciplines involved. In 2015, the scientific committee meeting was the occasion for a review of ANRS clinical trials and cohorts, and of the vaccine research program VRI/ANRS. In 2016, the meeting focused on virology research. At each meeting, the committee draws up a report on recommendations, and these reports are particularly useful for validating the scientific strategy and defining the outlook of the ANRS.

Exemplary mobilization of ANRS sites during the Ebola epidemic

The teams long involved in HIV research at ANRS sites were strongly involved in the response to the Ebola epidemic. Armed with their extensive experience in clinical research and a multidisciplinary approach, the teams were involved in 2015-2016 in clinical research and vaccine programs, in Guinea, in the framework of the Inserm program REACTing. Several studies in the human and social sciences were also set up.

Transmission, communication

Strengthened international cooperations

The ANRS has long cooperated with research institutions (NIH, NIAID, MRC, NIDA, DZIF, etc.) and international public health organizations (Global Fund, Unitaïd, WHO, UNAIDS, etc.). This is one of the cornerstones of the functioning of the ANRS and of the development of its actions, with a view to pooling resources and expertise. This is essential in facilitating and expediting the setting up of public policies based on scientific results. It is also instrumental in the international standing of French research, which should be promoted more. This is why the ANRS

management places particular emphasis on cooperation. As an example, in recent years, partnerships with Unitaïd were consolidated by conducting operational research in resource-limited countries. At the same time, an institutional collaboration was set up with the German infectious diseases network, notably the programs HIV Cure and HBV Cure.



ANRS driver of research



7 ANRS COLLOQUIA

- » annual meetings of the ANRS national viral hepatitis network
- » ANRS clinical research seminar
- » ANRS basic research seminar
- » ANRS HBV Cure workshop



5 SATELLITE SYMPOSIA

- » at IAS conferences
- » at French-language AFRAVIH conferences
- » at AFEF meetings

3 FRENCH-SPEAKING COMMUNITY EVENINGS

- » at CROI and EASL conferences



3400 RESEARCHERS, PHYSICIANS, PARTNERS

- » Brought together by the ANRS in 2015 and 2016

2 CO-PRODUCED BOOKS

- » Therapeutic management and follow-up of all people infected by hepatitis C virus (in French)(with the CNS and AFEF, 2016, Editions EDP Sciences)
- » Medical management of people living with HIV (in French)(with the CNS, 2016, Editions La Documentation Française)

ANRS extensive support for scientific events

34 COLLOQUIA

- » supported by the ANRS (€412 258)

6 PUBLICATIONS

- » supported by the ANRS (€36 500)

ANRS at the forefront of current events

30 PRESS RELEASES

- systematic media coverage of major scientific events: CROI, IAS, EASL, AASLD...
- monitoring of scientific publications and teams
- regular meetings with journalists
- press trips in the field

25 February 2015

HIV and tuberculosis: reassessment of current treatment regimens

Early administration of an antiretroviral to HIV-infected adults in Ivory Coast, plus 6-month preventive treatment of tuberculosis, significantly reduced the risk of severe morbidity. The final results of the ANRS 12136 TEMPRANO trial were presented at the CROI, in 2015.

20 July 2015

First case of prolonged remission in a child

Followed up in the framework of the ANRS French pediatric cohort, a woman now aged eighteen and a half who was infected by mother-to-child transmission at birth, is in virological remission even though she has taken no antiretroviral treatment for the last 12 years. This first case in the world was presented in Vancouver at IAD 2015 (8th IAS Conference on HIV Pathogenesis, Treatment & Prevention).

1 December 2015

African migrants: over one-third of infections occur after their arrival in France

The ANRS PARCOURS study showed that 35% to 49% of migrants from sub-Saharan Africa who are HIV seropositive and who live in the Paris-Île-de-France region were infected after their arrival in France.



1 December 2015

On-demand PrEP reduces the risk of HIV infection by close to 90%

The ANRS IPERGAY study showed that PrEP at the time of sexual relations reduces by 86% the risk of HIV infection in men who have sex with men. The study was published in the *New England Journal of Medicine* in December 2015, just after the French Ministry of Health announced its decision to authorize this new prevention tool in France.

19 July 2016

Treatment de-escalation: 4/7 days

Maintenance triple-antiretroviral therapy taken only four days a week instead of every day maintained viral load below 50 copies/mL in 96 of 100 patients of the ANRS 162-4D study. These results were presented at AIDS 2016, in Durban.

20 July 2016

Entry into the healthcare system: the challenge of Test and Treat

The ANRS 12249 TasP trial showed that repeated offer of HIV screening at home was well accepted by a rural population in South Africa. However, entry in the healthcare system is not sufficiently frequent or rapid for such an approach to reduce HIV transmission in the population. The results were presented at AIDS 2016, in Durban.

21 July 2016

West Africa: HIV prevention in men who have sex with men is the priority

Faced with a high risk of HIV infection, West African men who have sex with men could benefit from greater prevention, including pre-exposure prophylaxis. The first findings of the ANRS CohMSM study were presented at AIDS 2016, in Durban.



The scientific output in 2015-2016 of projects funded by the ANRS and performed by research institutions, universities, or hospitals, was stable. In 2016, 5.9% of ANRS publications were in the "top 1% of excellence," which is above the national average in the biomedical field. Over 58% of publications appeared in journals with an impact factor above 5. In 2015-2016, ANRS publications appeared in the following leading journals: *New England Journal of Medicine* (2), *The Lancet* (6), *Science* (3), *Nature* (5), *Cell* (4), *Immunity* (2), *Journal of Clinical Investigation* (3), *JAMA* (4), *PNAS* (4), *Blood* (7), and *PLoS Medicine/Pathogens* (14). In specialized journals, ANRS articles were published in: *Gastroenterology* (9), *Journal of Hepatology* (16), *AIDS* (34), and *Journal of Infectious Diseases* (27). Lastly, several plenary presentations were given by French researchers in large international congresses on HIV or hepatitis.

In France, in HIV research, 12 large clinical and/or basic research sites accounted for 70% of publications, 61% of publications were produced by teams in the Paris region and 39% by regional teams¹.

In the field of hepatitis, the distribution is more balanced between the Paris region and other parts of France. During this period, French teams participated greatly in major phase 3 clinical trials demonstrating the efficacy of new direct-acting antivirals in hepatitis C.

Internationally, bibliometric analysis shows that France continues in second or third position in the world, depending on the year, in HIV research (8.4% of publications worldwide) and in second position in hepatitis research (9.4% of publications worldwide).

RESEARCH	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
HIV basic research	119	110	135	123	159	131	150	131	143	139	118	122	117
Vaccine research	19	15	21	11	3	4	12	10	12	24	23	21	38
Public health, human sciences, and social research	21	24	40	36	47	48	34	36	40	36	41	38	44
Resource-limited countries	57	52	44	53	56	110	100	105	100	88	86	92	88
HIV clinical research	72	64	79	118	84	111	145	118	106	102	94	92	94
Viral hepatitis	18	28	34	89	77	76	147	148	131	127	116	123	144
Total	306	293	353	430	426	480	588	548	532	516	478	488	525

¹ In particular, in Lyon, Montpellier, Bordeaux, and Lille.

Human and financial means

The background features a collection of light gray icons. In the upper right, there is a cluster of stylized human figures of various sizes, representing a population or community. Below this, there are several financial charts, including a bar chart with varying bar heights and three pie charts, some of which are partially cut out.

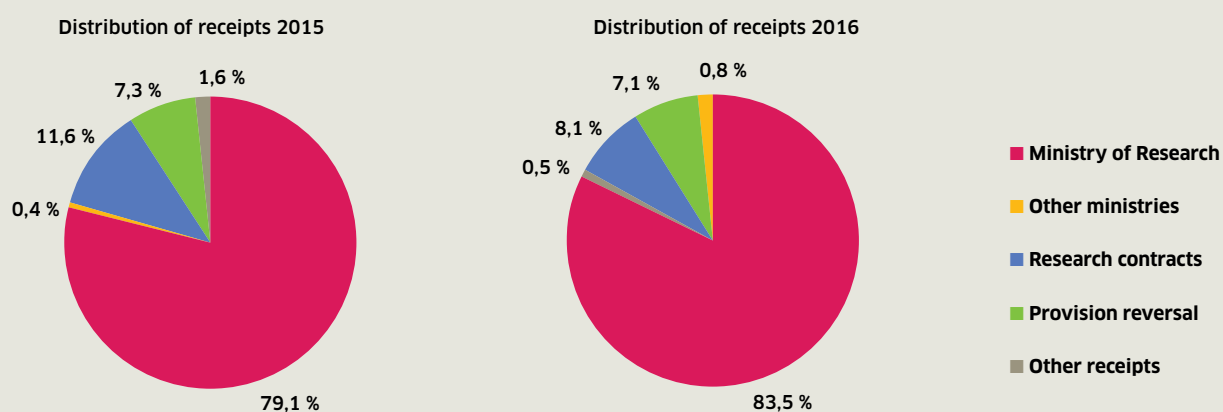
Human and financial means

ANRS resources

ANRS resources derive mainly from repeated support from the ministries represented on its board, completed by contractual resources accorded within the framework of research partnerships concluded with third parties (public or private) for the agency's scientific programs.

In 2015: receipts of €48.358 million

In 2016: receipts of €45.480 million



The ANRS is predominantly funded by public bodies, in line with its public service mission to run and fund research on HIV and viral hepatitis. This state support accounts for a steady 80% approximately of the agency's budget, mainly through recurrent subsidies from the Ministry of Higher Education and Research, which amounted to €38.3 million in 2015 as in 2016. The Ministry of Health provides steady funding of about €0.2 to 0.4 million per year, as a function of projects funded by the ANRS on the ministry's public health priorities. Lastly, the Ministry of Foreign Affairs and of International Development contributes to the ANRS by underwriting five international technical expert positions at ANRS research sites in resource-limited countries.

The revenue procured through research contracts concluded with public or private partners completes the financing of some projects that the ANRS alone cannot fund. This revenue, depending on the year, amounts to between 8 and 12% of the ANRS total and is essential when rolling out large-scale programs such as the RHIVIERA consortium and the HEPATHER cohort, and for ANRS-sponsored clinical trials, for which partnerships with the pharmaceutical industry must be maintained.

Lastly, the ANRS budget in 2015 and in 2016 included previously constituted reserves of €3.5 and €3.3 million, respectively. Other revenue from donations and bequests, and, for example, from leftover subsidies, amounted to 1 to 2% of total means.

Overall, various resources each year, plus credits that could be carried over from one financial year to the next, allowed the ANRS to have a total of open credits for its expenditure of €51.668 million in 2015 and €50.176 million in 2016.

94 % of means earmarked for research

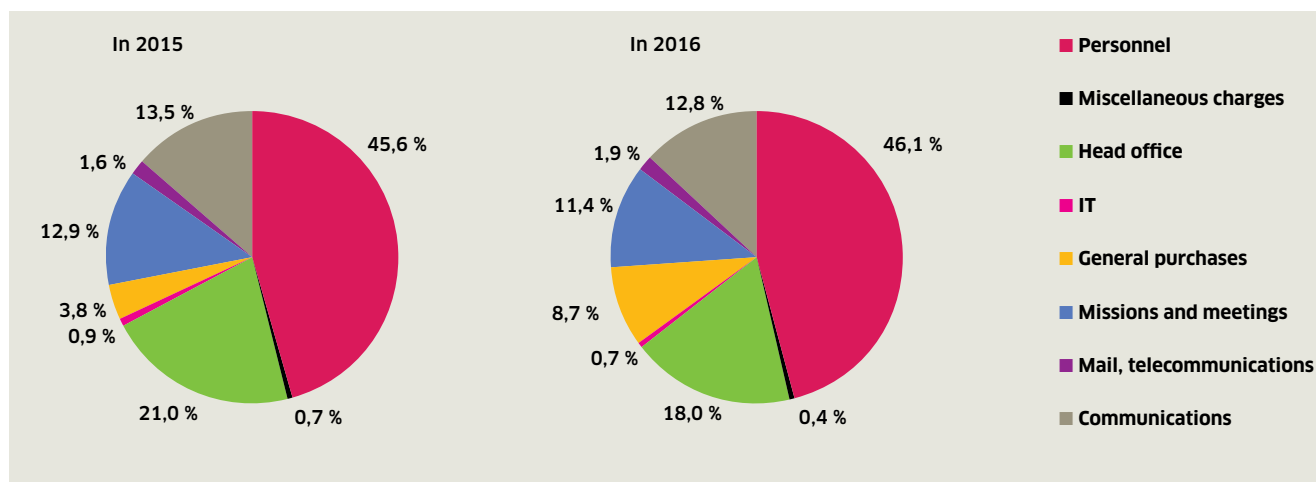
After approval by the Board, the ANRS means are each year distributed directly to the funding of research, in line with the agency's missions, and to the agency's operating costs.

The ANRS divides up the budget earmarked for research between research teams and service providers who implement the agency's scientific programs, in France and in resource-limited countries. Operational costs are devoted to the running of the ANRS head office in Paris.

The ANRS operating costs amounted to €2.838 million in 2015 (ie, 6% of the total budget) and €2.768 million in 2016 (ie, 6.3%). These costs were 5.6% below those of the period 2013-2014, thus freeing up more revenue directly available for research.

Therefore, almost 94% of the ANRS budget is directly invested in research.

Distribution of ANRS operating costs



The ANRS operating costs essentially cover personnel costs, expenses related to head office and its running costs (IT, telecommunications, mail, general supply items), the meetings of scientific committees and expert missions, and scientific information and communication activities.

With an average of €1.3 million per year, personnel costs are the greatest expense, with €2.8 million each year earmarked for running of the agency, ie, 46% of this budget. These personnel costs cover the remuneration of 22 of the 52 full-time equivalents of human resources employed at head office for the scientific and financial monitoring of research programs, scientific information and communication, and general administration of the agency. The 30 remaining full-time equivalents are made available to the ANRS by the organizations that are represented on its Board and which contribute an estimated €1.9 million a year. As this contribution is not financial, it is not included in the agency's budget. However, if it is taken into account, then it brings to €4.7 million a year the amount needed to run the ANRS, ie, a little under 10% of the total means available.

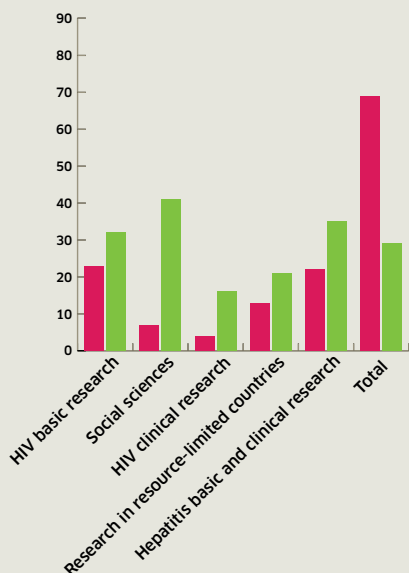


Research funding

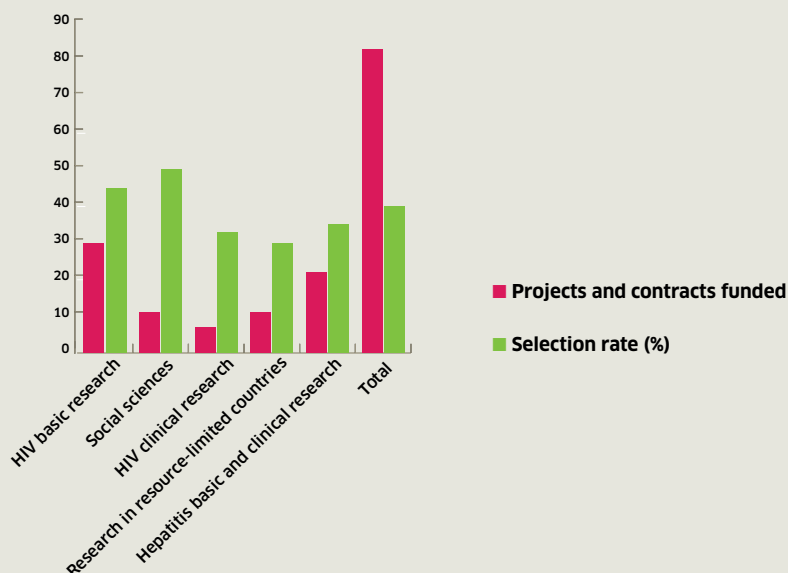
The funding of research, which accounts for almost 94% of the agency's means, operates on the basis of calls for research proposals. Each year, the ANRS announces two funding opportunities designed to select research projects and research contracts, as well as grants for young researchers. The ANRS also sponsors biomedical research. Clinical trials and cohorts are evaluated throughout the year in the framework of ANRS coordinated actions.

Research projects and contracts funded in 2015 and 2016

New research projects and contracts funded in 2015



New research projects and contracts funded in 2016



In 2015, the ANRS funded 69 new research projects and contracts out of 239 applications, ie, a selection rate of 29%. In 2016, 83 new research projects and contracts were funded out of 205 applications, ie, a selection rate of 40%.

Most of these projects were scheduled to run over a few years such that each call for proposals commits the ANRS for at least four financial years, for a total amount of €5 to 6 million, ie, additional financial commitment of between €10 and 12 million each year. Over 400 projects and grants were being funded during 2015 and 503 during 2016, 382 came directly from calls for proposals.

Distribution of research funding between HIV and hepatitis

Disease	2013		2014		2015		2016	
HIV/AIDS research	73,7 %	32,476 M€	69,7 %	32,315 M€	71,3 %	31,469 M€	74,9 %	30,975 M€
Hepatitis research	26,3 %	11,565 M€	30,3 %	14,026 M€	28,7 %	12,667 M€	25,1 %	10,394 M€
Total funding	100 %	44,041 M€	100 %	46,340 M€	100 %	44,135 M€	100 %	41,369 M€

The fraction of the ANRS budget earmarked for viral hepatitis increased until 2014, stabilized in 2015, and returned to its usual level of around 25% in 2016. The peak observed between 2013 and 2015 is mainly accounted for by the launch of the ANRS cohort HEPATHER, which recruited close to 20 000 patients over this period and which therefore needed a particularly high level of support. The cohort nonetheless benefited from the agency's own resources, without which this level of funding could not have been sustained.

Distribution by area of research

Areas of research	2013		2014		2015		2016	
Basic research	24,7 %	10,871 M€	24,4 %	11,300 M€	21,4 %	9,457 M€	23,2 %	9,600 M€
Clinical research	64,0 %	28,188 M€	61,7 %	28,606 M€	64,1 %	28,281 M€	66,6 %	27,545 M€
Public health, human sciences, and social research	11,3 %	4,983 M€	13,9 %	6,435 M€	14,5 %	6,397 M€	10,2 %	4,223 M€
Total funding	100 %	44,041 M€	100 %	46,340 M€	100 %	44,135 M€	100 %	41,369 M€

In 2016, the distribution of means by area of research, independently of the disease concerned, confirmed the trend observed in previous years, with clinical research accounting for two-thirds of the ANRS budget allocated to research.

The increase in public health, human sciences, and social sciences research leveled off at around 10% in 2016, as the ANRS IPERGAY study ended. In 2016, over half of the spending in this field concerned projects in resource-limited countries.

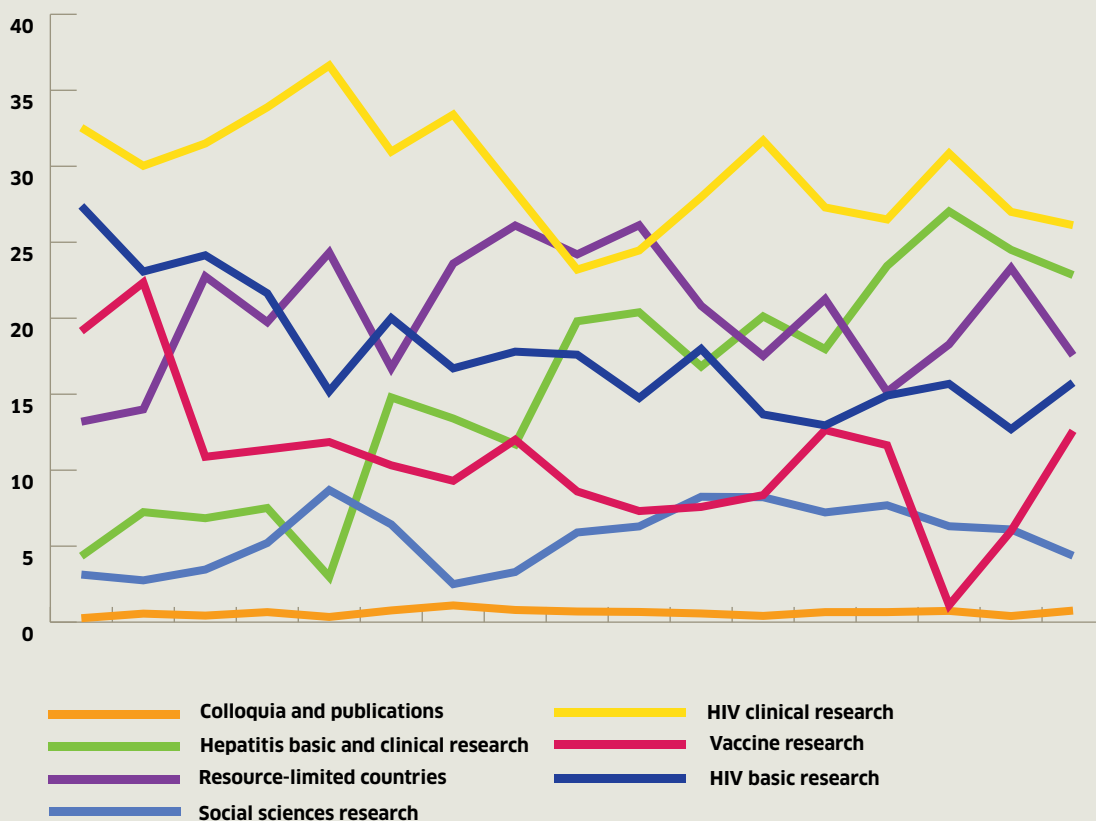
Lastly, in 2016, the proportion of funds allocated to basic research tended towards the level in 2015, a financial year marked by a drop in the number of projects proposed and approved in the framework of the calls for research proposals.



Distribution according to the seven scientific themes of the ANRS

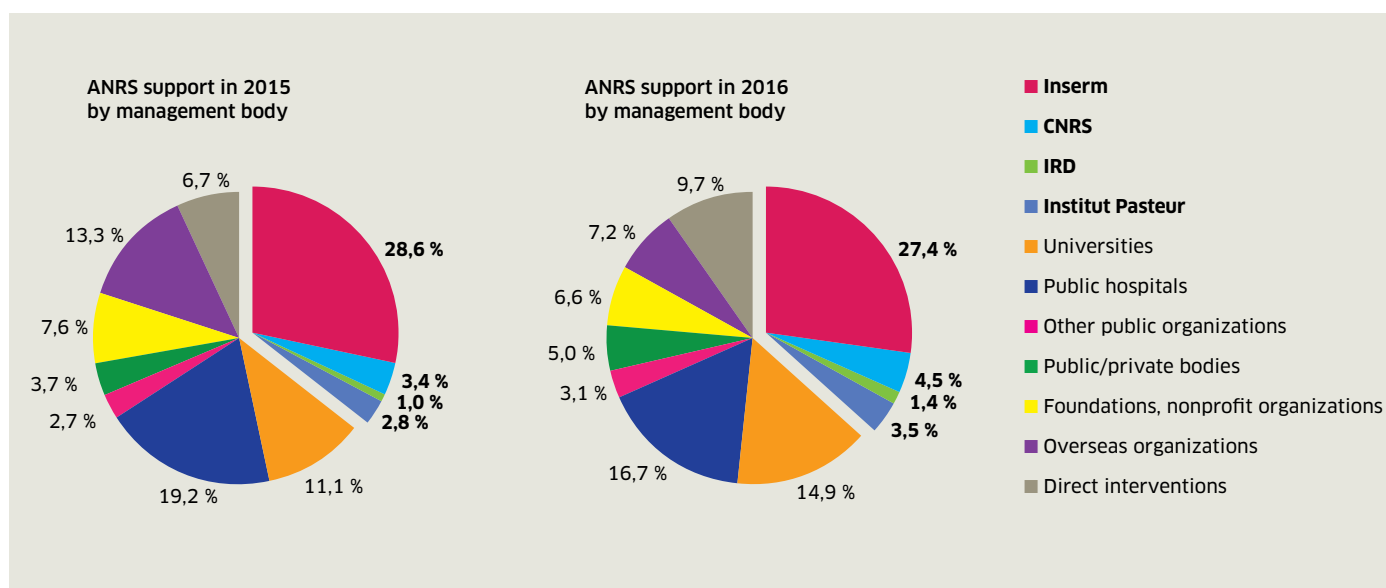
Operationally, the means allotted by the ANRS were distributed between the six scientific themes of the main areas of intervention, to which was added "support for colloquia and publications," which had a separate budget allocation. This subdivision by topic allowed earmarking of funds when the budget was voted, and also corresponds to the scientific departments of the ANRS.

ANRS expenditure according to field of research between 2000 and 2016



Organizations supported by the ANRS

As the ANRS does not itself conduct the research programs it finances, it distributes each year the bulk of its means between the main research organizations, in France and overseas, that actually run these projects.



In 2015, as in 2016, the four main stakeholders in the ANRS, ie, Inserm, CNRS, IRD, and the Institut Pasteur, received more than 36% of the agency's allocated support, with a marked preponderance for Inserm, which alone received 28% of the total support allocated. These proportions are consistent with the leading role these stakeholders play in the field of health research. Broadly speaking these proportions remain stable over time, including Inserm's share, which has not changed notably since the ANRS was incorporated into Inserm as an autonomous agency.

Universities and public hospitals are the second largest beneficiaries, each of them receiving a little more than 15% of the ANRS funding allocated each year. The support allotted to foreign organizations amounts on average to 10% of the total and essentially corresponds to direct interventions of the ANRS in resource-limited countries. The support paid to foundations and nonprofit organizations, ie, 7% on average, concerns research in resource-limited countries and in the developed world, and community-based research, notably in the field of prevention.

Lastly, with close to 10% of the total in 2016, support for "direct interventions" is not negligible and corresponds to expenses that the ANRS incurs for research projects in place of organizations unable to provide this funding. These expenses are notably related to the ANRS as sponsor: hospital surcharges, maintenance of biobanks that centralize sample collections, pharmaceutical service providers, and spending necessary for the production of experimental vaccines, in the framework of the Vaccine Research Institute (see page 55), the development of which is directly controlled by the ANRS.

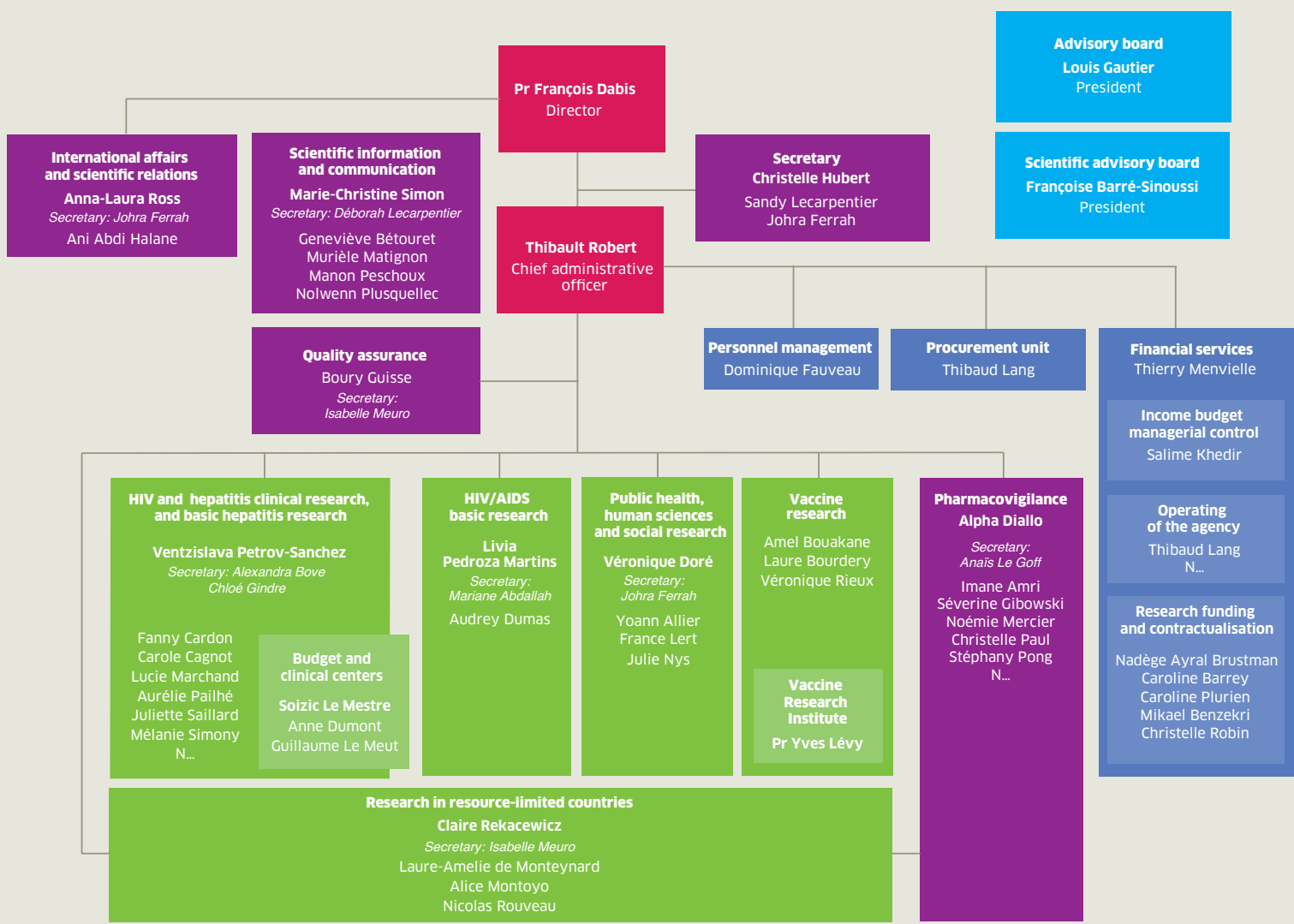
Calls for research proposals 2015

RESEARCH THEMES	CALLS FOR RESEARCH PROPOSALS AND SEED GRANTS										FELLOWSHIPS	
	Deposited			Selected			% selection			Deposited	Selected	% selection
	Projets	CI	Total	Projets	CI	Total	Projets	CI	Total			
Basic HIV research	65	7	72	18	5	23	28 %	71 %	32 %	63	19	30 %
Public health, human sciences and social research	12	5	17	4	3	7	33 %	60 %	41 %	15	5	33 %
HIV clinical research	22	3	25	4	0	4	18 %	0 %	16 %	6	2	33 %
Research in resource-limited countries	47	15	62	7	6	13	15 %	40 %	21 %	22	4	18 %
Viral hepatitis research	56	7	63	17	5	22	30 %	71 %	35 %	34	11	32 %
Total of calls for research proposals	202	37	239	50	19	69	25 %	51 %	29 %	140	41	29 %

Calls for research proposals 2016

RESEARCH THEMES	CALLS FOR RESEARCH PROPOSALS AND SEED GRANTS										FELLOWSHIPS	
	Deposited			Selected			% selection			Deposited	Selected	% selection
	Projets	CI	Total	Projets	CI	Total	Projets	CI	Total			
Basic HIV research	58	9	67	24	6	30	41 %	67 %	45 %	53	19	36 %
Public health, human sciences and social research	18	4	22	7	4	11	39 %	100 %	50 %	10	2	20 %
HIV clinical research	19	2	21	5	2	7	26 %	100 %	33 %	7	2	29 %
Research in resource-limited countries	31	6	37	9	2	11	29 %	33 %	30 %	14	4	29 %
Viral hepatitis research	49	9	58	23	1	24	47 %	11 %	41 %	35	13	37 %
Total of calls for research proposals	175	30	205	68	15	83	39 %	50 %	40 %	119	40	34 %





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