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Healthcare Investing for Life

CANDRIAM

A NEW YORK LIFE INVESTMENTS COMPANY

About
the author

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Manager of Candriam's award-winning biotechnology strategy since its inception in 2000, Rudi Van Den Eynde has headed our Thematic Global Equity Team since 2011. This Thematic Range also includes oncology, climate, circular economy, robotics, iInnovative technologies, demographics, and other thematic equity strategies.
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Megatrends.
What topic can experience more enduring change than *Healthcare*?
We know of physic gardens from the fourteenth century, and medical research written on papyrus has been dated from at least three millennia ago.
What we can be certain of is change, and progress.

World Cancer Day

Not waiting around for a magic solution

4 FEBRUARY

The COVID-19 pandemic ensured that in 2020 a lot of attention was paid to medical science. Many in the press predict that the breakthrough with the COVID-19 vaccines that use messenger RNA (m-RNA) technology will open the door to new cancer treatments. Do you agree?

It is true to an extent. In fact, m-RNA technology is already used in cancer research. To start with, the mass manufacturing of the m-RNA COVID-19 vaccines is based on biotech developments going back over 30 years, so it is not a brand new discovery. In healthcare research, specialists keep a very close track of discoveries in other areas as they know that new ideas and technologies get cross-fertilised all the time. There has already been some work to create an m-RNA-based cancer vaccine designed to instruct the body to produce a cancer-specific antigen that in turn would stimulate the immune system to target cancer cells. Unfortunately, this work has not been successful but the efforts to create m-RNA-based cancer therapies in the future continue.

The m-RNA technology has been tried to stimulate the immune system in its fight against cancer but this produced serious side effects. Also, once administered, m-RNA tended to end up in the liver. Unless the patient has liver cancer, it is important that m-RNA's delivery method is more targeted to the tumour itself, so much work will need to be done if this technology is to work.

We are monitoring very carefully the steady development of different immunotherapies, such as mRNA and many others, including more tried techniques such as antibodies in immune-oncology. There are many treatments for cancer but none are perfect. Cancer is not one disease but between 100 to 200 different cancers, depending on a system of classification. This complexity explains the unlikelihood of finding a one-size-fits-all solution. Instead, there are many different treatments, both existing and in development, some of them are used to complement each other, and none of them likely to invalidate the other.

So you are not sitting waiting for a wonder cure to invest in, but instead monitor research for new treatments that can enhance existing cancer therapies?

Exactly. For example, if you think about the big breakthroughs in oncology over the past decade, one was about the use of PD-1 inhibitors. With the original research into this was actually published in 2001[1], PD-1 inhibitors and PD-L1 inhibitors are a group of drugs designed to block the interaction between cancer cells and the human immune system. While these new treatments proved quite effective in their own, scientists discovered that they work best in combination with the very est ablished, old treatment - chemotherapy[2], at least for some cancers.

> **There are many developments that look very promising in pre-clinical tests but only clinical trials can determine if a drug offers real hope for patients.**

Our team has a lot of specialist knowledge in the field of medical science which we deploy to constantly analyse new drug developments, new screening tests and new tumour profiling methods. There are many developments that look very promising in pre-clinical tests but only clinical trials can determine if a drug offers real hope for patients. Therefore, we focus predominantly on clinical data to inform our investment decisions, alongside potential treatments' mechanism of action and their pre-clinical package. We only make meaningful investments in treatments that are backed by promising clinical data, even if it based on a relatively small number of patients.

Funding is much less of an issue compared to many years ago. Start-up companies that introduce real innovative solutions in our field usually do not have a problem with initial financing. First seed capital comes from smart venture capital investors, most of whom have very high levels of expertise and recognise the potential of particular innovations. Companies listed on a stockexchange also have an option for raising funds by issuing shares. And there are also many more specialised funds, such as ours, that fund strong research pipelines on behalf of their risk-aware investors.

What developments in the field of cancer treatment do you currently find most interesting as an investor?

One of the most interesting recent technologies is called targeted protein degradation. In our bodies we have a mechanism to destroy "obsolete proteins", which are at the end of their lifetime. Those old proteins carry markers (ubiquitins) which indicate to "protein cleaners" (proteasomes) that they are ready to be destroyed. Drug companies have learnt how to use this process to target the "cleaners" toward cancer cell receptors. In the past, antibodies were used to attack cancer cells but in cases when they are unsuccessful, doctors might be able to use protein degradation. We have seen some encouraging clinical data using this technology in the treatment of breast cancer. There are several companies working on this and we monitor them very closely.

There are also some encouraging new research in the field of antibodies. This is not a new area - the first antibody drugs for cancer treatment were approved in the late 1990s. Now, companies are working on the so-called "bi-specific" antibodies, which can attach our immune system's killer T-cells to the cancer cells. Based on recent clinical data, we think that this new technology will help many cancer patients, especially with haematological tumours.

Another ongoing developments are around a new treatment designed to block tiny pathways between cells that are used by cancer but are too small for antibodies to enter. However, scientists have learned how to block these pathways and drugs are being developed to target cancer without blocking any normal processes required for the normal functioning of the human body.

Doubtless, there will also be developments with m-RNA. However, as discussed, we should remember that sometimes there are different tools of achieving the same objective.

The difficulty in treating cancer is that cancer cells mutate very quickly and become more resistant to the treatment. To prolong the life of patients doctors require combination therapies or sequential use of totally different treatments. For some cancers a full cure may never be achieved. In those cases the aim would be to turn cancer from an acute into a chronic disease with subsequent treatments, winning the patient many years of extra life, with the least possible side effects. Every step we make in this long fight is a step towards better care, and every new drug approved is an improvement over what was possible before. The best thing we can do is to identify every gradual development that takes our treatments forward and help make the most promising of them happen.

Moreover, as an asset manager, we are committed to help in the fight against cancer beyond investments. Therefore, when we launched our Oncology strategy, we decided to donate 10% of the management fees retained by the fund to various non-profit research associations in the field of cancer treatments. We hope our donations will help build a healthier and more sustainable future for us all.

[1] https://blog.dana-farber.org/insight/2019/05/the-science-of-pd-1-and-immunotherapy/
[2] https://pubmed.ncbi.nlm.nih.gov/31535160/

In 2020, Gustave Roussy was recognised as a leading European institution in the fight against cancer and was ranked as the fifth Best Specialised Hospital in the world[1]. It is also one of the establishments supported by Candriam each year.

On the occasion of World Cancer Day, the Institute is launching Interception, a programme for prevention and screening tailored to individual cancer risks, and better treatments, as part of a General Practitioner-Hospital collaboration.

Presentation given by Doctor Suzette Delaloge, Programme Director.

In spite of the enormous progress in cancer treatment over the past 30 years, not only is cancer still the primary cause of death in western countries, but survivors continue to suffer after-effects. Prevention and screening are two major challenges for society.

The *Interception* programme aims – through early detection – to identify people most at risk from cancer and prevent the onset of the disease for them. As it is, some 30%-40% of cancers affect people who could have been identified as high-risk in the years preceding their diagnosis. Interception seeks to systematically offer them screening and personalised prevention. The long-term aim is not only to help them avoid serious cancers, but also to save them from the after-effects of cancer and cancer treatments.

Interception enables GPs, using customised software, to identify those of their patients who are particularly susceptible to certain cancers. Persons fall into the increased-risk-of-cancer category when the probability of their developing a given cancer is at least two-to-three times greater than that of the population at large; those, for example, with a genetic predisposition to the disease, those with precancerous lesions or those strongly exposed to toxic substances like tobacco.

The programme identifies these predispositions and offers these people a one-day consultation and information workshops. The programme also offers individual follow-up and personalised healthcare plans. In addition, if a cancer diagnosis is suspected, Interception takes immediate action.

Finally, *Interception* also provides for the subsequent monitoring of individuals through a simple annual online survey designed to obtain further information on patients, develop more knowledge of individual risks and assess the impact of the treatments offered.

Interception is a state-of-the-art prevention tool that will make earlier detection easier and increase the chances of curing cancers while mitigating their effects.

[1] From the rankings of the World's Best Hospitals 2021 as published in Newsweek.

World No Tobacco Day

Cessation of tobacco use: a civic-minded investment!

31 MAY

Tobacco is considered as the leading risk factor of many chronic diseases. It is, for example, the cause of one-third of all cancers. Without radical treatment, the best way to reduce the highly avoidable associated mortality is to quit smoking.

Lung, bladder, kidney, colon, liver, larynx... Sixteen different cancers, including some of the most aggressive forms of the disease, can be traced to tobacco products. They are also responsible for multiple debilitating if not deadly cardiovascular diseases. The risk of having a heart attack or stroke is doubled for smokers; cigarettes are the leading cause of severe respiratory diseases such as emphysema and chronic obstructive pulmonary disease.

The toll on human life is very heavy, particularly in developing countries. According to the WHO, tobacco use causes more than 8 million deaths per year worldwide. Although they make up seven out of eight deaths, current and former tobacco users are not the only victims of tobacco. Classified as a carcinogen some 20 years ago, second-hand smoke also does a lot of damage, including to children. According to the findings of a meta-analysis published in peer-reviewed journal Tobacco Control[1], exposure to second-hand smoke can increase the risk of developing oral cancer by 51%.

A major medical and economic cost

The medical and economic costs of tobacco use are by no means inconsequential, as demonstrated by the findings of the first benchmark study[2] conducted four years ago in 152 countries. The costs associated with hospitalisations and treatments were estimated at $422 billion in 2012, i.e. 5.7% of global healthcare spending. Total direct and indirect costs of tobacco use came out at $1,436 billion, i.e. 1.8% of international GDP, with four countries accounting for one-fourth of the total bill: China, India, Brazil and Russia.

Tobacco use is the
second-leading cause
of death in the world

65,000
children die each year from diseases attributable to second-hand smoke exposure

70-80%
of heart attacks in under-50s are due to tobacco

Tobacco is the
leading risk factor
of lung cancer.
It is 10-15 times higher in smokers.

Source: WHO

World No Tobacco Day: a determined movement

The first World No Tobacco Day was held on 31 May 1988, and the event has taken place on the same date each year for the least 33 years. The WHO and its partners systematically use this opportunity to spread information and raise awareness of the multiple risks associated with tobacco use. After focusing on heart disease, lung disease and protecting young people from being manipulated by the tobacco industry, the theme for this year is "Commit to quit!" In the run-up to the campaign, the WHO set a goal of helping 100 million smokers trying to quit. Under a support programme initiated in December 2020, it provides tools and resources aimed at helping them achieve their goal. In 2020, tobacco was the leading cause of death and debilitating illness around the world, with more than 10 million victims. As such, it was more lethal than AIDS, tuberculosis, maternal death, car accidents, suicide and homicide combined…

For health, economic and social reasons, competent authorities have launched an unbridled war against tobacco. In recent years, media campaigns, illustrated disclaimers, neutral packaging, advertising bans, establishment of a legal minimum age, tax and price hikes, and reduced numbers of smoking areas have proved effective in multiple countries. Some have even decided to take things one step further by permanently banning the sale of cigarettes to persons born after 2004. By implementing this emblematic measure, the New Zealand government clearly announced its ambition of becoming the first tobacco-free nation by 2025.

An incomplete and inadequate arsenal

Even as a public health priority, cession of tobacco use cannot be so easily decreed. According to the WHO, the guidance of a healthcare professional and use of appropriate medications double the chance of successfully quitting. Without adequate support, the failure rate is 96%. The fast-growing smoking cessation market can be divided into two categories: nicotine substitutes and pharmacological treatments. Several medications, such as bupropion and varenicline, are now recommended as treatments. More recently, cytisinicline was added to the existing treatment arsenal, though as-yet incomplete and insufficient to the task of overcoming the multiple failures and limiting relapses over the long term. Used as primary treatments, nicotine gum, lozenges and patches generate significantly inferior results compared to medications, especially among highly-dependent users.

Homeopathy, hypnotherapy, acupuncture… sometimes unconventional methods are preferred, but on the whole they have proved less effective. Due to a lack of irrefutable evidence, vaping devices (with or without nicotine) are not seen as a viable alternative. Scientific evidence is inconclusive at this point: given the lack of solid data indicating that they are effective and harmless, they cannot be confirmed as without danger.

New approaches

The discovery of a universal cure against tobacco dependency is the best hope for 1.3 billion smokers. For the last 20 years, researchers around the world have been working to develop an anti-nicotine vaccine. Multiple projects have been undertaken, but none has led to a successful outcome. Innovative avenues are currently being explored. One of the most promising comes from a US team at the Scripps Research Institute[3], which claims to have identified an enzyme capable of destroying nicotine in the blood before it gets to the brain. Tested on mice, their prototype is said to be reliable and will soon enter the human testing phase.

Progress is also being made on the technological front. Several mobile apps have been developed to help people quit smoking. One highly successful app, QuitNow!, provides arguments, advice, tips and games to keep the mind busy in moments of weakness. Developed by Spanish studio Fewlaps, it has already been downloaded more than one million times. At the very least, it makes up for one of the flaws often observed in the various treatment methods employed, by providing its users with constant personal support.

As drivers for change, investors will have a major role to play in the fight against tobacco use. In the interest of promoting public health, Candriam will be making its own contribution to this worthy cause. Relying on its team of experts, Candriam's ambition is to identify the most innovative companies capable of discovering and manufacturing the most effective developments, projects and solutions for the community.

[1] "Secondhand smoke exposure and oral cancer risk : a systematic review and meta-analysis", *Tobacco Control/British Medical Journal* (April 2021).
[2] "Global economic cost of smoking-attributable diseases", *Tobacco Control/British Medical Journal* (January 2017).
[3] "An enzymatic approach reverses nicotine dependence, decreases compulsive-like intake, and prevents relapse", *Science Advances* (October 2018

World Blood Donor Day

Giving blood: a vital need!

14 JUNE

Recent scientific progress could soon mean that haematological diseases may be curable, starting with certain blood cancers. Meanwhile, every blood donation counts…

Blood, plasma and platelet transfusions save millions of lives every year. These donations are used notably to satisfy urgent hospital needs, such as haemorrhages. They are also indispensable for the treatment of almost 150 haematological and oncological diseases, such as sickle cell anaemia and leukaemia, which represent one third of childhood cancers.

Characterised by a reduction in the quantity of red blood cells and/or an alteration in their quality, anaemia remains the most common blood disorder. According to the World Health Organisation (WHO), 1.62 billion people are affected, representing almost one quarter of the world's population.

An unusual discovery illustrates the relative lack of understanding of this topic however. Published in *The Lancet*[1], research undertaken in the US surprised the international scientific community. Septicaemia is a serious blood infection which appears to have caused some 11 million deaths in 2017. This estimation, which is twice the level accepted by specialists, would correspond to one death in every 5 worldwide.

Scientific progress

Genetic therapies are a veritable medical and technological innovation which have recently transformed the way in which certain blood cancers are treated. Two drugs are currently prescribed in the treatment of acute lymphoblastic B cell leukaemia and diffuse large B cell lymphoma, two rare but particularly aggressive forms of blood disorder. Know more commonly as CAR-T cells, their use is recommended for patients failing to react to traditional methods in a relapse situation.

3.4%
of deaths in the under-fives are associated with haemoglobin disorders

79%
of transfused patients in high revenue countries are over 60 years old

42%
of blood donations are collected in high revenue countries which represent less than 19% of the global population

54%
of transfusions carried out in low revenue countries are intended for children under 5 years old

100%
of blood supplies are provided by unpaid voluntary donors in 62 countries

Source: WHO

World Blood Donor Day: contributing to solidarity

The first World Blood Donor Day was held on 14 June 2004 and this event has been held every year for the past 26 years on the same date. The event is organised by the WHO and promoted by the Red Cross and Red Crescent international federations, the Blood Donor Organisations International Federation and the International Blood Transfusion Society. This major annual solidarity event is held to thank and encourage donors and to increase public awareness, and also to alert and mobilise governments around the world. This year's edition is running under the universal slogan "Give blood and keep the world beating". In addition to the traditional messages, this year's campaign is focusing more particularly on the role played by young people in guaranteeing a secure blood supply, ideally through voluntary unpaid donations. This year, the event will be centred in Italy. Many different events will be held around the country, notably in Rome.

According to available clinical data, the 12-month survival rate is quadrupled or even more. Several complete remissions have been observed as early as the first month of treatment. The first patient treated in the US about ten years ago is now fully cured. As a reflection of their immense curative potential, their prices have climbed to several hundred million dollars… for a single injection.

Genetic therapy may also prove its worth in treating haemoglobin disorders which affect more than 330,000 births per year, mainly in Africa. Among the most advanced projects, Vertex Pharmaceuticals and CRISPR Therapeutics are conducting promising clinical trials in beta thalassemia and sickle cell anaemia. The technique used enables the genetic defect to be identified, dissected, corrected and the modification to be inserted using molecular scissors. Presented at the American Haematology Society 62nd annual congress, the latest published results[2] display a significant clinical improvement which led to a reduction in transfusion dependence for the 7 thalassemia patients and the disappearance of vaso-occlusive crises for the 3 sickle cell anaemia patients. This genetic therapy using genome editing, which is soon to be tested on a cohort of 90 people, embodies an improved chance of a cure for millions of patients[3].

Several issues at stake

Despite the progress made in research, no drugs can replace human blood. According to the WHO, 118.5 million blood donations are collected annually. This level is considered "highly unsatisfactory" to respond to the increasing demand, exacerbated by the ageing population and also by the limited lifespan of blood products. Platelets last for 7 days, while red blood cells can be kept for 42 days and plasma for 360 days.

In order to combat this shortage, certain countries readily remunerate blood donors, including Switzerland, Austria, Russia and China. This strategy can sometimes prove efficient, such as in Germany, where one third of adults regularly give blood. Every US inhabitant can donate blood plasma 104 times per year, generating estimated earnings of 3,120 dollars. According to the *New York Times*, this "market" was valued at 21 billion dollars in 2017.

The principle of remunerating blood donations is contested and does not enjoy unanimous support. Behind the ethical questions, there are also questions over the traceability and security of donations. Led by the WHO, major international bodies recommend systematic screening for HIV, hepatitis B and C, and syphilis prior to any transfusion. They prefer building up reserves from voluntary unpaid donators, a group in which blood transmitted infections tend to be less prevalent in general. To achieve this goal, they invite the relevant authorities to launch awareness campaigns among populations, along with local blood collections and recruitment drives.

The search for artificial blood

Japanese researchers claim to have found the ultimate solution, asserting that they have created artificial blood from red blood cells and platelets. Published in the American magazine *Transfusion*[4], this discovery has several tangible advantages. The blood substitute is universal as it has been developed without antibodies or antigens. It can therefore be transfused to all patients, whatever their blood group. It can also be conserved at normal temperatures for over a year. The "prototype" which has been developed in a laboratory, has been tested on rabbits affected by a haemorrhaging disease. The results are

relatively conclusive: 6 of the 10 animals tested survived the experiment, which is a comparable success rate to natural blood transfusions. No side effects or coagulation problems were identified. The efficiency of the procedure in humans remains to be demonstrated and the manufacturing process needs to be industrialised.

The French biotech company EryPharma is also confronted with both of these challenges in its quest to produce red blood cells from cultures. EryPharma's promising technique would enable the group to develop the equivalent de 100 blood donations from one single stem cell sample. The company is confident and claims to have proof of a robust concept and hopes to begin mass production by the end of the decade.

Investors clearly play a major role in the development of technological, therapeutic and logistical innovation. Candriam, as a promoter of public health, will actively support the fight against all forms of haematological diseases. Through our network of experts, we will target the most promising projects and solutions in the stock markets.

[1] "A global accounting of sepsis", *The Lancet* (January 2020).
[2] "CRISPR-Cas9 gene editing for sickle cell disease and β-Thalassemia", *New England Journal of Medicine* (January 2021).
[3] 4 drugs treating sickle cell anaemia are currently authorised in the US. According to the FDA, this hereditary genetic disease affects 100,000 Americans and more than 20 million people worldwide.
[4] "Combination therapy using fibrinogen γ-chain peptide-coated, ADP-encapsulated liposomes and haemoglobin vesicles for trauma-induced massive haemorrhage in thrombocytopenic rabbits", *Transfusion* (July 2019).

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World Mental Health Day

Mental health: a priority investment area

10 OCTOBER

Population ageing and the consequences of the pandemic will significantly increase the prevalence of mental illnesses in the years to come. Investment will be essential to cover existing needs and develop new treatments, in particular against Alzheimer's disease.

Often reduced to psychiatric diseases, mental health actually covers a much larger field. Anxiodepressive disorders, developmental disorders, neurocognitive disorders, etc. A billion human beings could suffer from these disorders. Little known, underestimated and sometimes stigmatised, more than 500 mental ailments with various consequences are currently listed. According to the WHO, their prevalence continues to increase over time. The disease of the century, depression affects 350 million people a year. A rampant epidemic, dementia affects nearly 55 million people. As the population ages, dementia will affect 139 million people in 2050. In low- and middle-income countries, three-quarters of sufferers are not treated.

Social, economic and human costs

The social and economic costs of mental health are particularly high. According to the WHO, those directly linked to dementia reached USD 1.3 trillion in 2019. They are expected to double by 2030. A relatively optimistic estimate which does not take into account the many direct and indirect impacts of the pandemic, which are still difficult to accurately quantify (see box). The problem is not new. Two years before the health crisis, the National Institute of Mental Health had already highlighted the harmful effects of not taking care of mental health and drug addiction. The financial weight for American companies was then estimated at between USD 80 and 100 billion per year. At the same time, the National Alliance on Mental Illness estimated the loss of productivity of a worker with unresolved depression to be 35%.

The main international organisations are clear: mental health is a profitable investment. For every dollar invested in the large-scale treatment of common mental disorders like depression and anxiety, the gain in health and productivity is multiplied by five. Behind these strategic issues, mental health remains a cause of premature death. According to the WHO, the life expectancy of patients is reduced from ten to twenty years.

Improve prevention and screening

Although very different, serious mental disorders all have one thing in common: there is no cure. A number of treatments nevertheless succeed in reducing the symptoms, or even slowing down the degeneration process (see box). According to specialists, screening is currently the best way to prevent the onset of mental disorders, which is not always possible. In Parkinson's disease, the performance of clinical diagnosis at an early stage is estimated to be between 50 and 70%. A European study[1] nevertheless tends to show that a simple nasal swab test could detect the disease several years before the first symptoms appear.

Rapidly growing technological progress could contribute to this early detection. Among other levers, artificial intelligence should play a major role, as a study by the University of San Francisco suggests[2]. From a simple analysis of brain scanners, their algorithm can detect the presence of this disease six years before humans, on average. Another significant example: an algorithm being developed at a California university[3] is now able to detect three different forms of autism during pregnancy with 100% accuracy.

Alzheimer's: a first for twenty years!

A first since... 2003. Twenty years after the authorisation of the last treatment against Alzheimer's disease in the United States, the FDA approves a new drug. Officially approved last June, aducanumab has the particular ability to slow the cognitive decline of treated patients. Considered a breakthrough innovation, this human monoclonal antibody has benefited from an accelerated authorisation procedure, a privilege granted to products that provide significant therapeutic benefits compared to existing treatments. As a result of the numerous research work conducted in recent years, several drugs should soon complete the therapeutic arsenal: 126 molecules are currently in clinical development, including 28 in phase III. The health needs are considerable. They will increase further in the years to come, with population ageing and the impacts of the pandemic. According to the World Alzheimer Report, 100 million people will be affected by Alzheimer's disease in 2050, compared to 35 million in 2015.

New treatment avenues

Despite the difficulties encountered, research into mental illnesses is not slowing down. Some scientific projects are even charting new therapeutic perspectives. American and Hungarian researchers[4] in particular succeeded in balancing the communication between two types of neurons of the prefrontal cortex thanks to specific mRNAs. A major breakthrough that could lead to the development of new remedies for schizophrenia, depression and autism spectrum disorders.

On another issue, a team of researchers from the University of Copenhagen[5] may have found a way to cross the blood-brain barrier to allow certain neuroprotective compounds to reach the brain using nanoparticles. Successfully tested in mice, this discovery could radically improve the effectiveness of drugs used to treat epilepsy, Parkinson's and Alzheimer's.

Even more concrete, a molecule indicated for the treatment of symptoms of benign prostatic hyperplasia would decrease the chances of developing Parkinson's disease. According to the results of an observational study conducted in Denmark and the United States[6], the risk level would drop from 12 to 37%. Confident of their findings, researchers now want to confirm these results in a randomised clinical trial.

On the front line, investors will naturally play a decisive role in carrying out all of these projects. A public health actor, Candriam will identify and support the most relevant and useful initiatives for the community. Through its network of experts, it will promote companies that will produce the solutions of tomorrow.

[1] "Alpha-synuclein seeds in olfactory mucosa of patients with isolated REM sleep behaviour disorder", *Brain* (April 2021).
[2] "A deep learning model to predict a diagnosis of Alzheimer disease by using F-FDG PET of the brain", *Radiology* (November 2018).
[3] "Risk assessment analysis for maternal autoantibody-related autism (MAR-ASD): a subtype of autism", Molecular Psychiatry (January 2021).
[4] "Cell Surface Protein mRNAs Show Differential Transcription in Pyramidal and Fast-Spiking Cells as Revealed by Single-Cell Sequencing", Cerebral Cortex (July 2020).
[5] "Post-capillary venules are the key locus for transcytosis-mediated brain delivery of therapeutic nanoparticles", Nature Communication (July 2021).
[6] "Association of Glycolysis-Enhancing α-1 Blockers With Risk of Developing Parkinson Disease", JAMA Neurology (February 2021).

Mental illnesses: the impacts of the crisis

The direct and indirect impacts of the pandemic on mental health are still difficult to assess, but they have worsened an already precarious health situation, especially among children and adolescents. According to the WHO, there will be "long-term and far-reaching consequences". The first pieces of evidence are accumulating in the international scientific literature. Among other revelations, a study published in The Lancet Psychiatry reveals that people with psychotic disorders, mood disorders, addictions or mental retardation have a higher risk of developing a severe form of the disease. A source of disruption or interruption of essential mental health services, Covid-19 is also associated with the onset of psychiatric disorders, as shown by an Italian study. The pandemic will inevitably leave its mark on people around the world. According to a British study, 34% of recovered patients develop a neurological or psychiatric disorder within six months of infection.

World Diabetes Day

Diabetes: a silent and costly pandemic

14 NOVEMBER

14 November 2021 is an important day in the fight against diabetes as it marks the 30th World Diabetes Day. It comes at a time when the social, economic and human cost of diabetes is expected to explode in the coming years. Nevertheless, notable technological progress should help to improve the detection, monitoring and treatment of the disease.

Diabetes is a disease that concerns the assimilation, use and storage of sugars by the human body. It leads to hyperglycaemia associated with severe and even fatal metabolic disorders. This chronic endocrine disease takes two forms. Linked to hereditary genetic factors, type 1 diabetes is caused when the pancreas produces little or no insulin. It develops mainly in children, adolescents and young adults. Linked to a person's lifestyle, type 2 diabetes is caused by the misuse of insulin by the body's cells. It usually occurs after the age of 40 due to excessive weight, poor diet or lack of physical exercise. Type 2 diabetes accounts for about 90% of cases.

According to the International Diabetes Federation (IDF)[1], 463 million people - or one in eleven adults - are living with diabetes. However, half of those with diabetes are unaware of their condition. Undiagnosed and untreated, patients are exposed to disabling, if not fatal, complications (myocardial infarction, stroke, kidney failure, blindness, lower limb amputation, etc.). A silent and rampant pandemic, its growth curve will explode in the years to come. Diabetes will affect 578 million people by 2030 and 700 million by 2045.

1/11
adults are living with diabetes today: 463 million people

1/2
adults with diabetes are undiagnosed: 232 million people

1/5
people with diabetes are over 65 years of age: 136 million people

10%
of global health expenditure goes on diabetes, or $760 billion

79%
of people with diabetes live in a middle- or low-income country

1,110,100
children and adolescents under the age of 20 have type 1 diabetes

Source: Ninth edition of the IDF Diabetes Atlas (November 2019)

Direct, indirect and intangible costs

The social, economic and human effects of diabetes are considerable. Global health expenditure stands at $760 billion per year. Key indicator: the treatment of complications accounts for more than half of the direct costs. In the UK, the cost of treating an episode of diabetic acidosis is £1,387. By extension, premature deaths and disabilities account for more than a third of overall expenditure. In particular, absenteeism is seen as a factor of reduced productivity. A source of anxiety and discomfort, the numerous repercussions on the quality of life of patients are also to be considered. The direct, indirect and intangible costs of diabetes are exorbitant and set to increase. The IDF estimates that global health expenditure will reach $825 billion in 2030 and $845 billion in 2045.

Diabetes and its complications are a major cause of premature death: more than four million deaths each year, or one every eight seconds. Between a third and a half of these deaths are attributable to cardiovascular disease, of which diabetes is the direct cause. It should be noted that diabetes is now one of the ten leading causes of death in the latest WHO ranking. A highly symbolic figure, the number of deaths attributed to diabetes has increased by 70% in twenty years.

Technological achievements

The prevention of type 2 diabetes, which is partly preventable, is a top priority. The WHO recommends, in particular, a healthy diet, regular physical exercise and avoiding the consumption of tobacco. Weight loss is considered to be a key factor in delaying the onset of the disease and reducing its complications. Early detection also plays a strategic role.

Notable technological progress has opened up new perspectives in this area. An artificial intelligence system approved three years ago by the FDA can detect diabetic retinopathy with a 90% level of accuracy.[2] Another notable feature is that the machine produces an automated diagnosis that does not require the intervention of a health professional to interpret the images. This breakthrough is revolutionary and paves the way for further progress.

Many scientists are working to optimise the diagnostic offer, with promising results. Researchers at Queen Mary University of London recently succeeded in developing an AI that can measure the amount of fat around the heart, a predictive marker of the disease that is currently impossible to identify.[3] Based on a simple analysis of cardiac MRI images, this tool provides an answer in just three seconds. It may also be able to calculate the level of risk incurred by each patient.

New treatment alternatives

Despite considerable progress in research, there is no cure for diabetes. The standard treatment consists of the regular administration of insulin through insulin pens, inhalers or special pumps. Several second-line treatment drugs help to standardise the disease, which also needs to be monitored continuously through increasingly sophisticated blood glucose monitoring devices. New therapeutic avenues are currently being explored. They are mainly aimed at improving patient comfort. American researchers are working on a pill that could replace insulin injections.[4] Tested on pigs, this drug was found to be effective in reducing blood sugar levels in patients.

There are three other breakthrough innovations expected in the coming years, mainly in type 1 diabetes: the artificial pancreas, smart insulin and pancreatic islet transplantation. Already used in the United States and Canada for patients with unstable diabetes, this gene therapy has a major drawback that could soon be overcome. According to a team of American researchers[5], transplanting these pancreatic cells into the anterior chamber of the eye would do away with the need for immunosuppressors.

Driven by constant and growing demand, diabetes is a promising field of investment, underpinned by technological progress. Through its network of experts, Candriam will identify the most promising research projects. It will also support companies that produce the most useful medical treatments and devices for patients.

"According to the IDF, the direct cost of diabetes is expected to reach $845 billion per year by 2045.

[1] "IDF Diabetes Atlas", International Diabetes Federation (November 2019).
[2] "Pivotal trial of an autonomous AI-based diagnostic system for detection of diabetic retinopathy in primary care offices", *Nature* (August 2018).
[3] "Automated quality-controlled cardiovascular magnetic resonance pericardial fat quantification using a convolutional neural network in the UK Biobank", *Frontiers in Cardiovascular Medicine* (July 2021).
[4] "An ingestible self-orienting system for oral delivery of macromolecules", *Science* (February 2019)
[5] "Operational immune tolerance towards transplanted allogeneic pancreatic islets in mice and a non-human primate", *Diabetologia* (January 2019).

Diabetes: a dynamic market... driven by the United States!

One hundred years after the discovery of insulin and blood sugar control, the global diabetes market is reaching new heights. According to IQVIA, it reached $105 billion in 2020, an increase of 10.5% on the previous year. A notable fact: the United States represented 67% of sales, far ahead of the bloc of emerging markets, which accounted for a total of 11%. The diabetes segment is the second largest therapeutic area after oncology and made up 9.8% of the global pharmaceutical market, estimated at $1,174 billion. Another major finding was that two anti-diabetic drugs were among the top ten best-selling drugs last year. They appeared in sixth and seventh place in this ranking.

Note: all values are expressed in the manufacturer's price, excluding taxes.

Source: IQVIA (April 2021)

World AIDS Day

HIV: the end of the tunnel?

1 DECEMBER

Forty years after it first appeared, there is finally a realistic prospect of eradicating HIV using the combination of prevention and scientific advances. Research into a cure is making great strides, and we may have a vaccine in a few years too. As with other areas of medicine, investment will be a key driver for change.

The alert was raised on the 5th of June 1981. A rare form of pneumonia that was ravaging a gay district in San Francisco became the subject of an official communication from the Centers for Disease Control and Prevention (CDC). The human immunodeficiency virus was finally isolated two years later by two French researchers from the Institut Pasteur: Luc Montagnier and Françoise Barré-Sinoussi. Transmitted sexually, through blood, or breast milk from mother to her child, HIV causes a serious viral infection that gradually destroys the immune system. HIV causes AIDS, the Acquired Immune Deficiency Syndrome, which is the final stage of the disease. AIDS patients often acquire life-threatening secondary opportunistic diseases, such as candidiasis, tuberculosis, cerebral toxoplasmosis and Kaposi's sarcoma.

According to UNAIDS, in 2020 there were the total 37.7 million people who tested positive for HIV at some point in their life. Two-thirds of them lived in sub-Saharan Africa, which was home to most of those who died from AIDS last year globally (680,000 people died). The human toll is not insignificant, but it has halved over the past decade. Since the start of the epidemic, 36.3 million people died from AIDS-related illnesses.

37.7 milion
people are living with HIV

1.5 milion
new infections have been reported

680,000
people have died of an AIDS-related illness

27.5 milion
people have access to triple antiretroviral therapy

16%
of people living with HIV are unaware of their HIV status

66%
of people living with HIV have an undetectable viral load

Source: UNAIDS - Figures as of 31 December 2020

A priority area for investment

The Joint United Nations Programme on HIV and AIDS (UNAIDS) has set an ambitious goal of eradicating HIV by 2030. It hopes to achieve this by helping bring about a significant improvement in both HIV testing and in access to treatment, This would cover not only poorer countries but also their Western peers with the highest HIV infection rates.

As is often the case, investment will be one of the main drivers of change. Statistical modelling predicts that an annual investment of USD 29 billion is needed in low and middle income countries between now and 2025. Correctly invested, this money is expected to result in a very significant drop in the numbers of deaths and new infections.

However, UNAIDS has fallen behind on its programme targets whilst also having to contend with the Covid-19 pandemic. Closures and health restrictions have resulted in significant delays in diagnosis and treatment. People infected with HIV are more vulnerable from COVID-19 and have a risk of death twice as high as that of the general population. In many poorer countries, HIV positive people do not have access to COVID vaccines, especially in Africa.

A wide range of therapies

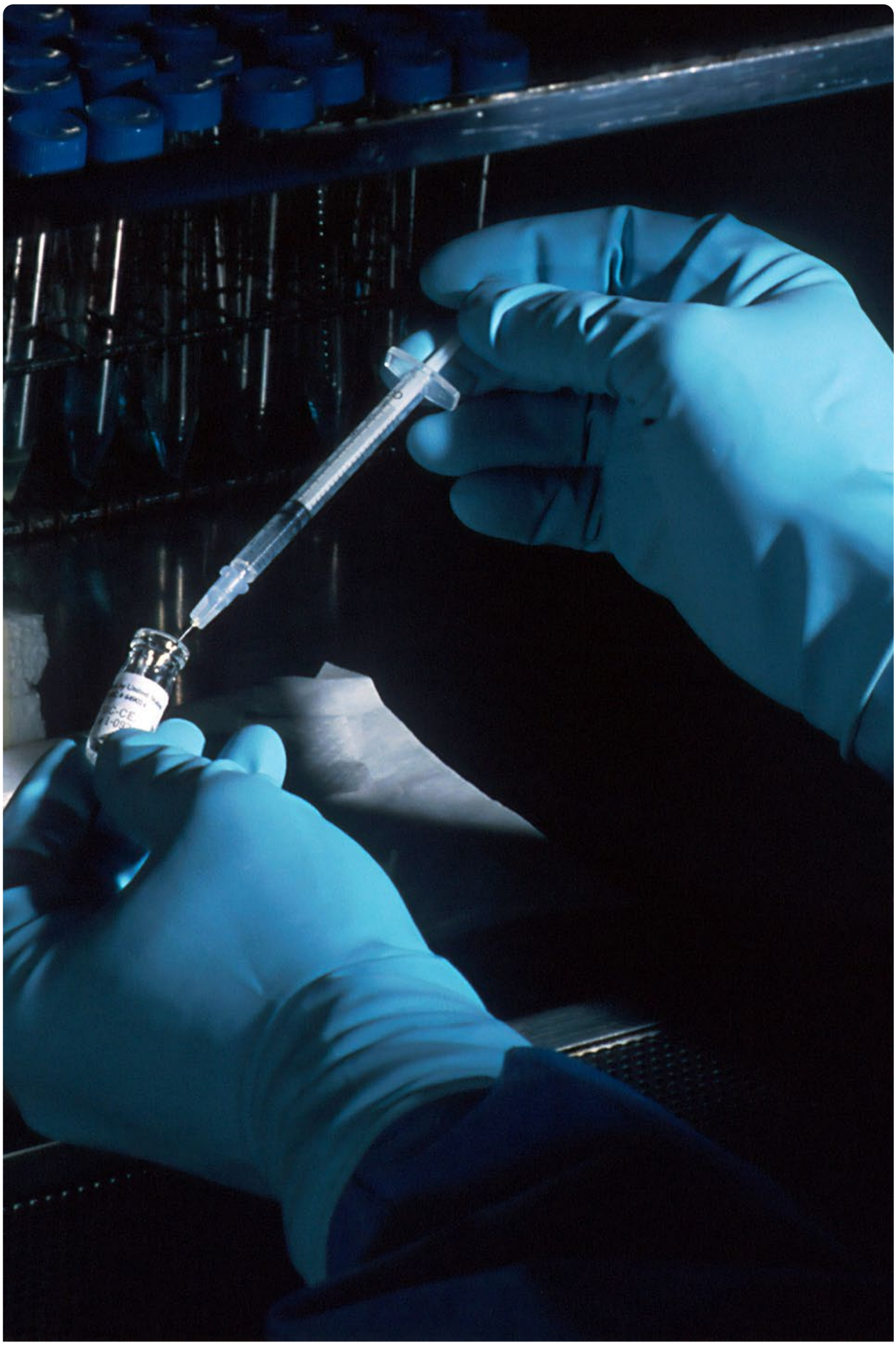
Thanks to advances in antiretroviral combination therapy, it has become possible for HIV positive people to lead a normal life, with their life-threatening disease. Several therapeutic options now make it possible to slow down its spread, but also prevent its appearance. Triple combination therapies have revolutionised care and are now the standard treatment for seropositive individuals. A combination of three antiretroviral molecules is used to block the replication of the virus and contain the viral load of patients, thus limiting their contagiousness. Treatments are also increasingly effective and cause fewer and fewer side effects. According to UNAIDS, 27.5 million people had access to such therapy last year, or nearly three-quarters of the target population.

Where there is a risk of possible transmission, post-exposure prophylaxis started within 48 hours after exposure and taken diligently for 28 days can prevent the virus from taking hold. Conversely, pre-exposure prophylaxis prevents any infection. Composed of two antiretrovirals, it is intended for seronegative populations at high risk, such as injecting drug users or members of the LGBT community. If it is administered before and after contact, its clinical efficacy is estimated at 99%.

Productive pharmaceutical research

A radical pharmaceutical development could soon remove the major constraint of having to take daily medication. Recently approved in the United States and Europe, a long-acting injectable dual therapy can now be prescribed to patients stabilised on daily oral therapy. As it involves a bimonthly treatment, it should significantly improve the quality of life of patients. The EMA (European Medicines Agency) is currently reviewing another injectable medication that could soon be approved for use in patients whose treatment has failed due to multi-drug resistance. Taken every six months, it would be used in combination with one or more antiretrovirals. Pharmaceutical research is fairly active in this area and is not merely limited to just these two therapeutic innovations. Prolonged-release tablets, auto-injectors, subcutaneous implants are some of the concrete solutions currently in the pipeline.

In addition, a vaccine for HIV could also become a reality in the coming years, notably thanks to messenger RNA technology. A long-awaited clinical trial was also recently launched. Phase I is scheduled to last two years, i.e. until April 2023[1].



> **79.3 million people have contracted HIV since the start of the epidemic.**

Promising leads

Scripps Research and International AIDS Vaccine Initiative have a head start. At the end of the first clinical phase, their vaccine candidate reported a 97% efficacy. Based on the stimulation of specific immune cells, the technique could even be used against other viruses. Less advanced but no less promising, a range of different research projects are ongoing. They include encouraging research into a vaccine consisting of antibodies genetically modified using molecular scissors[2]. Based on compelling evidence in mice, it could prevent HIV infection. Drug research is also making great strides. Researchers at the University of Utah have developed an injectable drug capable of preventing and curing people with HIV[3]. Successfully tested on primates, human testing is due to start in the near future.

[1] "A Phase 1 Study to Evaluate the Safety and Immunogenicity of eOD-GT8 60mer mRNA Vaccine (mRNA-1644) and Core-g28v2 60mer mRNA Vaccine (mRNA-1644v2-Core) », ClinicalTrials.gov (August 2021).
[2] « Vaccine elicitation of HIV broadly neutralizing antibodies from engineered B cells », Nature Communications (November 2020).
[3] "Dual CD4-based CAR T cells with distinct costimulatory domains mitigate HIV pathogenesis in vivo", Nature Medicine (August 2020).

Confirmed case of a second person cured of HIV

The news caused a stir in the international scientific community. A British patient is now considered as the second case of functional remission from HIV infection. After receiving a stem cell transplant at the end of 2017, Adam Castillejo was able to stop taking his antiretroviral treatment and has not relapsed. Confirmed thirty months later in The Lancet*, this great victory over the disease was nevertheless tarnished by the death of the famous "Berlin patient". Declared cured by his doctors ten years ago after a double bone marrow transplant which had allowed him to become seronegative, the American Timothy Ray Brown succumbed to cancer unrelated to his previous HIV infection. He died on 30 September 2020 at the age of 54.

(*) "Evidence for HIV-1 cure after CCR5Δ32/Δ32 allogeneic haemopoietic stem-cell transplantation 30 months post analytical treatment interruption: a case report", *The Lancet HIV* (March 2020).

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