The Virus Hunters: Banishing the Scourge of AIDS

written by Natalia Drozdiak
In a documentary film on the renowned photographer Robert Mapplethorpe, the actress Isabella Rossellini vividly recalls her first meeting with the artist a year before his death. Mapplethorpe’s gaunt and wasted body, she remembers, was collapsing from AIDS “in a way you don’t really see anymore.” Like many other victims, Mapplethorpe had contracted the virus before any advanced drugs were on the market. Before the anti-AIDS drugs, the HIV virus could spread freely in the body and develop quickly into the finishing stroke called Acquired Immunodeficiency Syndrome (AIDS) — the effects of which Rossellini so intensely remembers seeing in Mapplethorpe. Later generations, however, were luckier.

It was only in 1987, six years after the disease was first discovered, that the first anti-AIDS drug, AZT (azidothymidine), came on the market. Since then, progress in the field has soared and a variety of more advanced drugs have come to replace AZT as the best option for treatment. Thanks to the successful partnership of three scientists — Antonín Holý, Erik De Clercq and John Martin — a new generation of effective anti-HIV/AIDS drugs have enabled victims to lead full and relatively normal lives. In a major contrast to Robert Mapplethorpe’s time, a person who is HIV-positive today and who is treated properly can, according to De Clercq, “live with the disease, until he or she dies of other diseases.” The disappearance of the gruesome images of emaciated AIDS victims in recent years demonstrates the remarkable progress in treatment that these three men have pioneered.

The first collaborations between the scientists stretch as far back as May 1976, when the Belgian virologist Erik De Clercq first met the Czech chemist Antonín Holý at a conference in Göttingen. The conference, which was held at the Max-Planck Institute for Biophysical Chemistry, featured Holý’s presentation on biologically active nucleic acids. After Göttingen, De Clercq, who was based at the Rega Institute for Medical Research at the University of Leuven, wrote to Holý in Prague to tell him if there were any nucleosides worth exploring for antiviral activity that they should be sent to him. Soon thereafter, Holý (who was based at the Institute of Organic Chemistry and Biochemistry) sent De Clercq three different compounds. After months of research, De Clercq reported back to Holý with positive results, noting that one of the nucleoside analogues, DHPA, exhibited remarkable antiviral activity against DNA and RNA viruses like herpes simplex, measles, vaccinia and vesicular stomatitis. This discovery led to the publication of their path-breaking nucleoside study in the May 1978 issue of the journal Science and marked the start of their long and fruitful partnership.

Holý and De Clercq in San Francisco in 1993 after a visit to Gilead Sciences
Three years later, in 1981, the AIDS disease was first reported in a publication in MMWR magazine as “Kaposi’s Sarcoma and Pneumocystis Pneumonia among homosexual men.” It was quickly established that the disease was not as rare as initially thought, nor was it reserved exclusively for the homosexual community. The infections spread swiftly, while the nature of the disease remained uncertain until 1984, when the HIV virus was finally isolated. With the virus isolated, more effective treatment could then be researched and developed. Antonin Holý and Erik De Clercq’s previous studies on DNA and RNA viruses laid the foundation for what would become invaluable breakthroughs in the field of HIV/AIDS research.

By 1985, the successful work of Antonin Holý and Erik De Clercq attracted contract proposals from the American pharmaceutical company Bristol-Myers, now known as Bristol-Myers Squibb. The company’s interest in their work brought the two scientists together with John C. Martin, who at the time was the Associate Director of the Anti-infective Chemistry Department at Bristol-Myers. After the HPMPA compound and other phosphonate derivatives were described in various publications, the three began collaborating in 1987 on the production of the crucial anti-viral drugs. Holý helped John Martin synthesize these acyclic nucleoside phosphonates — the most important of which included HPMPA, cidofovir (HPMPC) and adefovir (PMEA). These compounds were then sent to Erik De Clercq for analysis. He compared the test results to Holý’s initial compounds and also specified which phosphonates should be developed to fight which diseases. In the results, De Clercq remarked that HPMPC (or cidofovir) is like both DHPA and HPMPA in that it can fight herpes virus infections, including cytomegalovirus retinitis, but is even more efficacious and less toxic. Of HPMPC’s sister nucleoside, PMEA (or adefovir), he noted that it should be developed to treat HIV/AIDS since it “inhibits retrovirus infections with a potency that is 25-fold greater, and a selectivity that is 5-fold greater, than that of azidothymidine (AZT).”

The actual development of the drugs only began once John Martin moved to Gilead in the fall of 1990. Martin, who was the new Vice President of Research and Development at Gilead, brought the phosphonate collaboration along with him. In September of 1991, Gilead CEO Michael Riordan, Erik De Clercq (Director of the Rega Foundation in Leuven) and Karel Martinek (Director of the Institute of Chemistry and Biochemistry in Prague) all signed an agreement to transfer the licensing for the HPMPA collaboration from Bristol-Myers over to Gilead Sciences. The license covered the existing phosphonates HPMPC (cidofovir) and PMEA (adefovir), as well as all the phosphonates that would follow, including the most important one, PMPA (or tenofovir).
With the new license, Gilead went straight to developing cidofovir to treat herpes, pox, adeno and papillomaviruses, and cytomegalovirus retinitis, in particular. (CMV retinitis is a virus that affects the retina and is often seen in late-stage AIDS patients). The cidofovir drug, Vistide®, was approved for the market in 1996, and it was due to its success that Gilead could begin marketing the next anti-viral treatment, Viread®.

Meanwhile, in March of 1992, when Gilead was still considering development of PMEA (adefovir) as its next drug, De Clercq (after conversations with Holý and Martin) noted that PMPA should be considered as the next best substitute to PMEA for the treatment of HIV. The phosphonate PMPA, known as tenofovir, was first described a year later in 1993. In the end, tenofovir was actually preferred to adefovir for the treatment of HIV since the PMEA compound was deemed too toxic for long-term use against HIV. At a lower dosage, however, adefovir is very suitable to fight hepatitis B, so Gilead developed it into the drug Hepsera®, which was released in 2002. Yet, given the urgency for effective HIV treatment, the development of tenofovir was the first priority. The development of a drug usually takes more than ten years, but Viread®, or tenofovir disoproxil fumarate (the form in which tenofovir can be taken orally), was out on the market by 2001 — faster than normal. This was due to high demand for the drug, but also because several clinical trials had already proved the drug to be effective.

Now more than 75% of all HIV patients (and 90% of those who have never been treated before) are treated with Viread® or a combination thereof. These are not surprising numbers since, even today, tenofovir is still the most successful agent on the market to prevent HIV from reproducing. Tenofovir is most effective when combined with other compounds, but alone it can already reduce the amount of HIV-infected cells in the blood while increasing the number of virus-fighting immune system cells.

It is these crucial T-cells (the immune system cells designed to clear foreign pathogens) that the HIV virus targets.

* Products, resulting from the Holý-De Clercq collaboration and commercialized by Gilead*: (photo courtesy of Gilead Sciences, Inc.)

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  1) Vistide®: cidofovir
  2) Viread®: Tenofovir disoproxil fumarate (TDF)
  3) Hepsera®: Adefovir dipivoxil
  4) Truvada®: combination of tenofovir disoproxil fumarate (TDF) with emtricitabine
  5) Atripla®: combination of tenofovir disoproxil fumarate (TDF) with emtricitabine and efavirenz
  6) Complera®: combination of tenofovir disoproxil fumarate (TDF) with emtricitabine and rilpivirine
  7) Stribild®: combination of tenofovir disoproxil fumarate (TDF) with emtricitabine, elvitegravir and cobicistat
Once the body is infected, the virus works in three stages. In the blood cell, the virus first converts its own RNA into DNA, a process that requires an enzyme called reverse transcriptase. The viral DNA then integrates itself into the human DNA with the help of the integrase enzyme. In the final stage, new copies of the viral proteins are cleaved off via the protease enzyme, allowing the viral proteins to leave the cell and to spawn elsewhere. Most drugs only attack one stage of the virus by inhibiting the protease enzyme, which stops the multiplication of the virus but leaves infected cells intact to roam throughout the body. These drugs tend to have a destructive effect on the body because they also inhibit the production of healthy T-cells.

The virus will often mutate and then develop resistance to the drug — a process which can take as little as six months. Tenofovir works differently because the body will not easily develop a resistance to it, nor will it kill off healthy T-cells. The drug works by simulating the shape of one of the four nucleotides, or building blocks, of DNA. During the first stage of the HIV virus cycle, the virus takes the drug to be a building block from which it can make DNA and weaves it into its own DNA strand. Like a Trojan horse, once inside, the drug can then inhibit the virus’ reproduction process.

This essential compound, tenofovir, is available in three different Gilead drugs that treat HIV. Viread®, which came out in 2001, was the first and main form of the drug, while Truvada®, which came out three years later in 2004, combines tenofovir with the emtricitabine compound. Atripla®, came out in 2006 and contains three different classes of compounds (tenofovir with emtricitabine and efavirenz) in a single pill. Atripla® is also the first daily single-tablet regimen for the treatment of HIV. These drugs are so effective that the continued use of them will make the HIV-count in the blood practically immeasurable. In the more than ten years since Viread®’s inception, studies have also shown that the treatment does not cause any serious side effects — a major breakthrough in HIV treatment.

Professor Erik De Clercq has proudly claimed that, with the continued use of these drugs, one can “keep the HIV in a ‘prison’ for one’s entire life.” Although, the patient must be diligent about taking the drugs in order to ensure that the virus will not replicate, this treatment has allowed for HIV patients to live normal lives. This is a major advance in treatment compared to what was offered in the 1980s. Of the tenofovir compound, Prof. Zdenek Havlas, the former Director of the Institute of Organic Chemistry and Biochemistry in Prague, has said, “with its low toxicity, and no resistance from the body against it ... tenofovir truly is a miracle drug, something quite like the philosopher’s stone.”

De Clercq, Brosgart and Martin. Brosgart was instrumental in the development of adefovir for the treatment of hepatitis B.
At an event on HIV treatment and innovation hosted by the California Health Institute in 2009, the Gilead CEO John Martin spoke of the collaboration’s groundbreaking discoveries. “These are phenomenal things”, Martin said, “[...] to think that we have gone from HIV being a death-sentence 22 years ago [as late as 1987], to having 3-drug therapy 13 years ago [in 1996], to now being able to treat it with a single pill [with Atripla®] ... to have so many people in the developing world on therapy ... and to be thinking about a prevention.” The achievements of this collaboration are indeed phenomenal, and the progress in HIV treatment, which the three scientists have initiated, seems to show no sign of slowing down.

The prevention treatment that Martin referred to is the PrEP (pre-exposure prophylaxis) with Truvada®, which has since been approved by the United States Federal Drug Administration on July 16, 2012 as the first and, as yet, only chemical used for preventing HIV infections. The day is especially memorable as it also coincided with the untimely death of Antonin Holý.

If the treatment is taken several days before and after exposure, the drug can interfere with the virus’ ability to copy itself and spread. When taken properly, the treatment can lower the risk of HIV infection by over 90%. Truvada opened up a whole new era for public health strategies. In cities such as San Francisco Truvada now goes hand in hand with advocacy for prevention. The city’s board of councilors recently decided to provide Truvada to all at-risk residents who requested it, regardless of their ability to pay.

The positive findings of the PrEP study lead many to believe an HIV vaccine is within grasp. John Martin points out that “over the past 25 years, scientists have always said ‘a vaccine is less than a decade away’ [...] but nothing concrete has been discovered and they are still saying it.” Given the nature of the virus to constantly mutate, both John Martin and Erik De Clercq consider the development of an HIV vaccine in the near-term to be unrealistic. Although the vaccine is an important long-term research goal, for the near future, it is perhaps more useful to look at ways to improve treatment, or even ways in which the virus can be eradicated so that a person does not have to depend on life-long treatment. Gilead is currently undertaking research in both of these areas.

In fact, Gilead has already found ways in which their successful drugs might be improved for certain target groups. In September 2011, the company came out with a new anti-AIDS drug that combines tenofovir and emtricitabine with rilpivirine, a compound discovered by Erik De Clercq’s former colleague Dr. Paul Janssen. The development of this Gilead HIV drug came out of an agreement with the company Tibotec of Johnson & Johnson. (Tibotec is a Belgian company that developed the compound rilpivirine and was founded by Rudi Pauwels, a former student of Erik De Clercq’s.) The advantage of rilpivirine is that it is safer and better tolerated. This would be a preferred alternative to Atripla® for HIV-positive women of childbearing age, since one of the compounds in Atripla®, efavirenz, can cause birth defects.

Pauwels was instrumental in setting up a novel AIDS assay system.
Janssen, who died in 2003, began developing rilpivirine in 1986 with initial help from De Clercq. It was around this time, when John Martin was still at Bristol-Myers, that Martin asked De Clercq which compounds — Holý’s or Janssen’s, nucleosides or non-nucleosides — he thought were the best. Erik responded “both!” without hesitation. In what is a great highlight in the Belgian partnership with Gilead, these compounds are now combined.

In 2012, the California-based-company reached a new milestone with Stribild. The drug combines four active ingredients: tenofovir, emtricitabine, elvitegravir and cobicistat. But TDF will soon be replaced by another tenofovir prodrug called tenofovir alafenamide or TAF. The new drug is even more potent than the former tenofovir or TDF, allowing the doses to be 10 times less concentrated. This further reduces the risk of any side effects of tenofovir and would bring the treatment of HIV/AIDS within the grasp of a perfect treatment regimen.

There are roughly 35 million people in the world infected with HIV, but thanks to the Gilead drugs (and those about to be produced), the HIV virus does not necessarily have to take a turn for the worse and develop into AIDS. For this reason, Zdenek Havlas of the IOCB, like many others, is more concerned with the increasing rate of hepatitis B infections.

If there are 35 million infected with HIV, hepatitis B (or HBV) infections have reached ten times that number — approximately 350 million. The virus itself is much stronger than HIV, and can survive in most temperatures. Yet, what is most shocking about the hepatitis B virus is that it can be stealthily active in the body for twenty years, without any signs or symptoms, before the patient might suddenly die of liver failure. Although a vaccine for hepatitis B exists, it is not very effective since it does not protect a minority (approximately 10%) of those vaccinated.

The adefovir drug Hepsera® came out in 2002 to treat hepatitis B but, in this case also, tenofovir has become the preferred method of treatment due to its lower levels of toxicity. (Viread® was also licensed to treat hepatitis B in 2008). Unlike with the HIV virus, however, 10% of Hepatitis B victims who take Viread® for five years at an early stage have been able to rid themselves of the virus. Although these patients could easily relapse and therefore still need to monitor the disease, these are already very impressive numbers in the fight to treat and contain hepatitis B infections.

The original compound, HPMPA, which was discovered through the collaboration of Antonin Holý and Erik De Clercq, has since provided hundreds of other acyclic nucleoside phosphonates that continue to grow into innovative treatments. Because many similarities have been found between the activity of a virus and the activity of cancer, other phosphonates from the same family are already being developed as ways to treat cancer. The human papillomavirus (HPV) for example, has been linked to cervical cancer, but can be completely eradicated with the treatment of some of these other compounds. More studies have also shown the efficacious use of the phosphonates to treat non-Hodgkin’s lymphoma in dogs. A cancer cure for humans based on these phosphonate derivatives is now within reach.

The collaborative work of Holý, De Clercq and Martin has been revolutionary in the field of medicine. It is clear that the foundation of this success is grounded in their teamwork. As Antonin Holý was quoted as saying in an article in Der Spiegel from 1996: “I would be nothing without De Clercq, but De Clerq would also be nothing without me. And [John Martin at] Gilead was ‘the cherry on top’. To that end, the drugs have three rightful fathers.” In their acceptance speeches in 2009, when Antonin Holý and Erik De Clercq received Honorary Doctorate degrees from the University of South Bohemia in the Czech Republic, they both partly dedicated their awards to John Martin.
“Without his unshakeable faith in these discoveries”, Holý said, “we would have accomplished nothing.” It is most impressive to see how each man is careful to give the other their due credit — a modesty that is rare in the scientific and academic worlds.

Within the past quarter century, the collaborations of these three dedicated scientists have revolutionized HIV treatment and saved the lives of millions of HIV-infected people. Thanks to their accomplishments, the image of emaciated AIDS victims wasting away in agony, like that of Robert Mapplethorpe and countless others, has become a relic of the past in the Western world.

The scientists' concern for the less affluent victims of HIV led to an agreement signed in 2010 whereby both the University of Leuven and the IOCB of Prague waved the royalties established in the name of Antonin Holý and Erik De Clercq in favor of HIV patients in 112 developing countries. Gilead Sciences thereby became the first innovator pharmaceutical company in 2011 to join the Medicines Patent Pool (MPP) and expand access to its medicines through the sharing of drug patents. The MPP was established by UNITAID, a Geneva-based global health organization that works to make high-quality, life-saving treatments and diagnostics more affordable in low-income countries. Gilead’s agreement with the MPP covered tenofovir/TDF in 2011 and was expanded in 2014 to include tenofovir/TAF. More people in the developing world than those newly infected are now receiving life-saving treatment for HIV/AIDS. These statistics inspire the hope that the HIV/AIDS pandemic which has claimed the lives of more than 30 million people since the 1980’s will be brought under control even in poorer countries.
Prof. Erik De Clercq:

Erik De Clercq’s successful career in Virology began as a medical student at the University of Leuven, Belgium where he received his MD in 1966 and his Ph.D. in 1972. Over the years, he worked his way up to be Chairman of the Directory Board of the Rega Institute at the University. He has received numerous honorary doctorates, professorships and awards for the discoveries of antiviral agents. In 2001, the European Union awarded both De Clercq and Holý the René Descartes Prize for Scientific and Technological Excellence in European Collaborative Research. In 2008, The European Patent Office and the European Commission elected De Clercq as European Inventor of the year. In 2010, along with Dr. A. Fauci, De Clercq was awarded the Dr. Paul Janssen Prize for Biomedical Research. De Clercq lays claim to over 2,500 publications, one of which is a paper titled “Toward Improved Anti-HIV Chemotherapy: Therapeutic Strategies for Intervention with HIV Infections” that was published in 1995 in the Journal of Medicinal Chemistry and has been recognized by the ISI (Institute of Scientific Information) as a citation classic. Erik De Clercq is a member of several editorial boards and was also the editor-in-chief of Antiviral Research as well as the book series Advances in Antiviral Drug Design. He is a member of the World Health Organization Expert Advisory Panel on Virus Diseases and in 1988, also founded the International Society for Antiviral Research. As a professor, he has taught courses in a wide variety of subjects including cell biology, biochemistry, microbiology and virology for students of medicine, dentistry and biomedical science. His friend and scientific collaborator Antonin Holý knows how much De Clercq loves to lecture and since he “was aware from [his] own experience of the high quality of [De Clercq’s] lectures”, arranged for De Clercq to lecture at the Charles University, the Jihočeská University (České Budějovice) and the Palacky University (Olomouc) in the Czech Republic after he had to retire from the University of Leuven.

Dr. John Martin:

After completing his Ph.D. in organic chemistry at the University of Chicago, John Martin started his career in nucleic acid research and drug development at the pharmaceutical company Syntex. At Syntex, where he stayed from 1978 to 1984, he co-invented ganciclovir, a drug that treats cytomegalovirus. In 1984, Martin moved to Bristol-Myers as the new Director of Antiviral Chemistry where he started collaborating with Erik De Clercq and Antonin Holý on the acclaimed anti-AIDS drugs. In 1990, John Martin moved out to California to work for Gilead Sciences, a pharmaceutical company that had just started up three years before in 1987. There he started as the company’s Vice-President for Research and Development. The same year, he received the Isbell Award of the American Chemical Society for applications of carbohydrate chemistry to the design of medicinally active nucleosides and nucleotides. John Martin is currently the Chairman of the Board of Directors at Gilead and is also the Chief Executive Officer, a position that he has held since 1996. He has also been a member of several other boards, including the board for Gen-Probe Incorporated, the Presidential Advisory Council on HIV/AIDS and Chairman of the Board for the California Healthcare Institute. John Martin is the recipient of the Gertrude B. Elion Award for Scientific Excellence from the International Society of Antiviral Research and, in 2008, was inducted into the National Academy of Engineering.
Prof. Antonin Holý:

In 1963, Antonin Holý received his Ph.D. in organic chemistry from the Charles University in Prague and, since then, has worked as a research scientist at the Institute of Organic Chemistry and Biochemistry. Before continuing on in his collaboration with Erik De Clercq and John Martin to develop the anti-AIDS drugs with Gilead, he took part in the original procedures for the preparation of azidothymidine (AZT)—the first anti-AIDS drug on the market. He also discovered the compound for the anti-herpetic therapeutics Duviragel®, which was produced by the Czech company Léčiva. In 1986, he received the Czechoslovak National Prize for Chemistry for the discovery of the "Acyclic Nucleoside and Nucleotide Analogs" that led to the development of the Gilead drugs. By 1987, he was named head of the Department of Bioorganic Chemistry at the IOCB. In 1994, he was promoted to the position of Director of the IOCB, which he maintained until 2002. In 2001, along with Erik De Clercq, he received the Descartes Prize from the European Union and then, in 2003, the Czech State medal “Pour merit”. He was nominated by the Czech Academy of Sciences for the Nobel Prize of Medicine in 2009. A year later, in 2010, the Secretary General of the European Union proclaimed Holý to be an Ambassador of Excellence. With over 60 patents and 700 publications, Antonin Holý has also been awarded numerous Doctor honoris causa degrees from various Universities. In 2004, he published his own book in the Czech language titled Principles of Bioorganic Chemistry in the Design and Development of Antiviral and Anticancer Drugs. He died at age 75 in Prague, Czech Republic in 2012.