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Review

In search of a selective therapy of viral infections☆

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ABSTRACT

This article is meant as an introductory chapter to the special issue of Antiviral Research on "Twenty-five years of antiretroviral drug development: progress and prospects", commemorating the first description of azidothymidine (AZT) as an antiretroviral agent. This has prompted me to highlight some of the hallmarks that played an important role in my own search of a selective therapy of viral infections: i.e., the induction of interferon by double-stranded RNA [such as poly(I)·poly(C)], allowing the cloning and expression of β-interferon; the discovery of the reverse transcriptase (RT) (and HIV as a retrovirus depending for its replication on RT), allowing the identification and development of a wide variety of RT inhibitors, nowadays used for the treatment of AIDS; the specificity of herpesvirus inhibitors such as acyclovir and BVDU, in the treatment of HSV and VZV infections; the role of acyclic nucleoside phosphonates (tenofovir, adefovir and cidofovir) in the treatment of HIV, HBV and DNA virus infections; and that of the NNRTIs (leading from TIBO to rilpivirine) as an essential part of the current anti-HIV drug cocktails. This article forms part of a special issue of *Antiviral Research* marking the 25th anniversary of antiretroviral drug discovery and development, vol. 85, issue 1, 2010.

This article provides a personal account of my own remembrances concerning the search of a selective therapy of viral infections during the past 40 years; it is intended for publication in the special issue of Antiviral Research on "Twenty-five years of antiretroviral drug development: progress and prospects", commemorating the first description of azidothymidine (AZT), as an antiretroviral agent in the October 1985 issue of PNAS (Mitsuya et al., 1985).

In my crusade, or should I say, odyssey, towards the development of a selective therapy for viral diseases, I started my wandering tour in 1967, 1 year after I graduated as Medical Doctor (MD) from our University, with the search for specific inducers of interferon. Interferon had been discovered, now more than 50 years ago, in 1957 by the late Alick Isaacs and by Jean Lindenmann (Isaacs and Lindenmann, 1957), but for many years it remained a rather esoteric principle, rather than a real molecule, so that, occasionally, interferon was referred to as "misinterpreton" (Lindenmann, 2007).

But, those that believed in interferon, as did my mentor and adviser, Prof. Piet De Somer, saw in interferon the panacea for the treatment of all virus infections, just as penicillin had believed to be the panacea for the treatment of bacterial infections. For many years, the anticipated potential of interferon to prevent and/or treat viral diseases remained hypothetical, if not controversial, and many scientists (particularly chemists) even doubted whether the interferon "molecule" really existed.

The fact that interferon could be induced by double-stranded (ds)RNAs, such as poly(I)·poly(C) (Field et al., 1967a,b; Lampson et al., 1967; Tytell et al., 1967), as demonstrated by Maurice Hilleman's group at Merck, generated, as I recall from these early days (1967), an enormous impact. On the one hand, it indicated that interferon really existed, and, on the other hand, it suggested that interferon could be produced in high yield by using inducers such as dsRNAs (De Clercq, 1974). Studies on the mechanism of induction of interferon by poly(I)·poly(C) revealed that the poly(I) strand was more important than the poly(C) strand (De Clercq and De Somer, 1971). The biological role of double-stranded (ds)RNAs in natural defense mechanisms against virus infections was in the 1970s a focus of attraction (Carter and De Clercq, 1974), antidating by 30 years what in 2005 would be heralded as the world of RNA interference (Mello and Conte, 2004).

In 1980, in a joint effort between the Laboratories of Walter Fiers (Ghent), Jean Content (Brussels) and our Laboratory (Leuven), using poly(I)·poly(C) as the inducer, we succeeded in cloning and expressing β-interferon in prokaryotic cell systems (Derynck et al., 1980a,b). Co-induced, together with β-interferon, was β-2-interferon (Content et al., 1982), a molecule that later on would be known as IL-6 (interleukin 6).

While β-interferon would find its way to the market for the treatment of multiple sclerosis, α-interferon would become the standard care (in combination with ribavirin despite their

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shortcomings in terms of costs and side effects) for the treatment of hepatitis C (De Clercq, 2009a). Poly(I)·poly(C) itself never became a "medicine", but the mismatched derivative thereof, poly(I)·poly(C_{13},U), has still survived, under the name "ampligen" as a potential antiviral drug (De Clercq, 2009a). Ampligen has proved to be effective, if used prophylactically against some experimental flavivirus and picornavirus infections in mice (Leyssen et al., 2003; Padalko et al., 2004) and has been considered for a long time as a potential treatment for CFS (chronic fatigue syndrome), a disease which may have a putative viral origin.

Double-stranded RNAs, as represented by poly(I)·poly(C), have in all these years remained the paradigm for new discovery in molecular biology, going from antisense oligonucleotides (Van Aerschot, 2006), to ribozymes, and then small interfering (si)RNAs, which represent the latest version of dsRNAs and are now widely acclaimed for their therapeutic potential, not necessarily for the treatment of virus infections (Tan and Yin, 2004) but for any diseases that could profit from silencing problematic genes.

In 1970 – I had just returned to Leuven after a 2-year fellowship in the Laboratory of Prof. Thomas C. Merigan at Stanford University, where I had worked on the mechanism of induction of interferon by the poly(I)·poly(C) type of interferon inducers – I was incited by the discovery of the reverse transcriptase by Temin and Baltimore (Baltimore, 1970; Temin and Mizutani, 1970) [1975 Nobel Prize for Medicine or Physiology to Howard Temin and David Baltimore, shared with Renato Dulbecco]. This discovery proved the existence of the enzyme responsible for the reverse transcription, or transcription from RNA to DNA, a process that had been predicted in the 1960s by Temin but generally met with disbelief. The discovery of the reverse transcriptase counteracted the prevailing thought or central dogma of molecular biology dictating that the genetic flow of information would go from DNA to RNA and not the other way around. The reverse transcriptase would ultimately become the most important target enzyme for the treatment of AIDS, but this could hardly be predicted in 1970, since AIDS, as a disease was only recognized in 1981, and the causative agent thereof, HIV-1 (originally named HTLV-III and LAV-1), was first described in 1983 (Popovic et al., 1983; Barré-Sinoussi et al., 1983) [2008 Nobel Prize for Medicine or Physiology to Françoise Barré-Sinoussi and Luc Montagnier, shared with Harald zur Hausen].

A few months after Temin and Baltimore had reported direct evidence for the existence of the reverse transcriptase (RT), I had the assay working in our Laboratory in Leuven, and started my search for inhibitors of the enzyme. [From the interferon field I had learned that interferon could be induced with double-stranded RNAs such as poly(I)·poly(C) and single-stranded RNA being the template for RT, it seemed logical to look for a competitive inhibitory effect of other polyanionic substances on the RT activity.] This led to the discovery of suramin (in 1975) as an RT inhibitor (published in 1979) (De Clercq, 1979) (on the specific recommendation of "Bob" Gallo to whom I had mentioned this discovery in 1978). In the 1970s, the general belief was that the reverse transcriptase would play a role in the origin of cancer whether virus-induced or not. So, it was logical that I was anxious to find out whether suramin had an inhibitory effect on cancer. I examined its activity in an experimental mouse leukemia model in mice. It had no effect, and this may have been the end of the story, but in the US, at NIH, Sam Broder (who later would become head of NCI) followed up on my earlier description of suramin as an RT inhibitor (De Clercq, 1979), and showed it to be active against HIV *in vitro* in cell culture (Mitsuya et al., 1984), and also to be effective *in vivo* in a small number of AIDS patients (Broder et al., 1985). In the treatment of AIDS, suramin would soon be superseded by other and more potent agents such as azidothymidine (3′-azido-2′-deoxythymidine, AZT) (Mitsuya et al., 1985), which, in turn, would later be superseded by tenofovir (PMPA) (De Clercq, 2008) [for a comparative evaluation of PMPA *versus* AZT in the prevention of simian immunodeficiency virus (SIV) infection in monkeys, see Tsai et al., 1995].

Azidothymidine (AZT) was already licensed for clinical use (as zidovudine) against AIDS in 1987, that is 2 years after its anti-HIV activity was reported. Ironically, I had a chance to look at the antiviral potential of 3′-azido-2′-deoxythymidine (AZT) and various other 2′,3′-dideoxynucleoside analogues (De Clercq et al., 1980a), which had been sent to me by Fritz Eckstein [with whom I had been collaborating on interferon induction by double-stranded thiophosphate derivatives when being in Tom Merigan's Laboratory at Stanford], but this was at the end of the 1970s, and neither AIDS nor HIV (HTLV-III or LAV-1) had been discovered by that time [and at the end of the 1970s interest in antiretrovirals targeted at the RT was rapidly waning] so that I missed a unique opportunity to come up with the antiretroviral potential of AZT. Shortly after Mitsuya et al. (1985) had described AZT, followed by the 2′,3′-dideoxynucleosides ddI and ddC (Mitsuya and Broder, 1986), we (Baba et al., 1987) were the first to describe the anti-HIV activity of 2′,3′-dideoxy-2′,3′-didehydrothymidine (d4T) (synthesized by Piet Herdewijn in our Laboratory). This compound was also described by Lin et al. (1987) and would later be known as stavudine for the treatment of AIDS (see Martin et al., 2010).

Suramin, which based on my original observations as inhibitor of the RT of murine leukemia virus (De Clercq, 1979), was the first anti-HIV agent to be described to be active against HIV both *in vitro* and *in vivo* (as reviewed by De Clercq, 1987), was later shown to inhibit HIV replication primarily by inhibiting its adsorption to the cells rather than by inhibition of the HIV RT (Schols et al., 1989). In addition to suramin which can be described as an hexasulfonate, various other polyanionic substances, such as dextran sulfate (Baba et al., 1988; Mitsuya et al., 1988) would later be identified as virus adsorption inhibitors. Polyanionic substances (such as the naphthalene sulfonate polymer PRO 2000) have remained potentially useful as topical microbicides to prevent vaginal HIV transmission (De Clercq, 2009a).

In 1976, together with my good friend Paul F. Torrence (with whom I had been collaborating for several years on interferon induction by double-stranded RNAs), I attended in Göttingen (Germany) a meeting at the Max-Planck-Institut für Biophysikalische Chemie (3–5 May 1976), organized by the late Karl-Heinz Scheit, on synthetic nucleosides, nucleotides and polynucleotides. There I met several highly distinguished nucleic acid chemists, all pioneers in their field, i.e. John Moffatt, John Montgomery, Nelson Leonard, Helmut Vorbrüggen, Wolfgang Pfleiderer, Willy Guschlbauer, David Shugar, Fritz Eckstein (the latter two I had collaborated with and I knew from before), and I still wonder where I got the courage (or "guts") to mingle up, as a medical doctor (MD), with such exquisite, exclusively chemical, companionship. In retrospect, this meeting had a decisive impact on my career, and, more importantly, on the collaborations and friendships which originated from my "chemical" encounters in Göttingen.

Thus started my collaboration with Richard T. ("Dick") Walker, with whom I would later organize three NATO Advanced Study Institutes, the first in 1979 (Sogesta, Italy), the second in 1983 (Les Arcs, France) and the third in 1987 (Il Ciocco, Italy). From these NATO Advanced Study Institutes emanated the ICARs (International Conferences on Antiviral Research), of which the first (then not yet called the first, as we did not know there would ever be a second one) was held in Rotterdam (The Netherlands) in 1985, the second in Williamsburg (Virginia) in 1988, the third in Brussels in 1990, the fourth in New Orleans in 1991, ... and the twentieth in 2007 in Palm Springs, the twenty-first in Montreal (Canada) in 2008 and the twenty-second in Miami Beach (Florida) in 2009.

But, let us return to 1976 when I met with Dick Walker in Göttingen and decided to try to develop specific antiviral agents: this was at a time the only antiviral agents known were IDU (idoxuridine),

TFT (trifluorothymidine), ara-A (adenine arabinoside) [which were all active against herpes simplex virus (HSV), albeit displaying little selectivity in their antiviral action], amantadine (active against influenza) and ribavirin (a broad-spectrum antiviral agent). [Also in 1976 Rich Whitley and his colleagues were the first to report on the efficacy of an antiviral agent, vidarabine (ara-A) in the systemic treatment of herpes zoster (Whitley et al., 1976)]

In the "old days", no ethical committees or stringent FDA rules existed to regulate the clinical use of antiviral drugs, simply because there were not any antiviral drug candidates. Herbert ("Herb") Kaufman was a pioneer (of some sort) in that he switched, almost overnight, when studying antiviral compounds from the rabbit eye to the human eye. With the help of the ophthalmologists Prabhat Maudgal and Luc Missotten, I did the same by introducing, in 1980, BVDU (brivudin) for the topical treatment of herpetic eye infections (Maudgal et al., 1980a,b, 1981b). But, we went one step further; in 1980, we also introduced BVDU in the systemic treatment of herpes zoster (De Clercq et al., 1980b; Maudgal et al., 1981a), thus following the footsteps of Whitley et al. (1976) on vidarabine, the first antiviral agent to be used systemically for the treatment of herpes zoster. The use of vidarabine for the treatment of VZV infections has, in the mean time, been discontinued. That of BVDU has still continued in large parts of the world, and contributed to alleviating the symptoms in thousands of patients suffering from herpes zoster, worldwide.

Just after I had started my collaboration with Dick Walker [and his boss, Prof. A.S. ("Stan") Jones], which led to the discovery of BVDU (brivudin) as a selective and potent anti-HSV-1 agent (De Clercq et al., 1979) and which later would become a useful medicine for the treatment of herpes zoster (De Clercq, 2004), two papers appeared, in December 1977 in the Proc. Natl. Acad. Sci. USA (Elion et al., 1977) and in March 1978 in Nature (Schaeffer et al., 1978), announcing the selective anti-HSV activity of acyclovir, based on the specific recognition of acyclovir as a substrate for the HSV-induced thymidine kinase [in 1988 Gertrude Elion and George Hitchings would receive the Nobel Prize (shared with James Black) for Medicine or Physiology for this (and other) discoveries].

Why was this an important development ? For several reasons: *first*, in the late seventies we had initiated a project on new acyclovir derivatives and in 1983 we demonstrated that acyclovir could be derivatized to its more water-soluble amino acid esters (Colla et al., 1983), one of which, the valine ester or valaciclovir [valaciclovir (Valtrex®, Zelitrex®)], has now replaced acyclovir, in the oral treatment of HSV infections. *Second*, the dependence on the virus-induced thymidine kinase also proved to be a key issue in the activity of BVDU (brivudin), which is currently on the market as (one of) the most effective drug(s) for the treatment of varicella-zoster virus (VZV) infections, i.e. herpes zoster (shingles), and has been licensed for clinical use in many parts of the world (trade names: Zostex®, Brivirac®, Zerpex®).

The collaboration I had started with Dick Walker was continued with his former co-worker, Chris McGuigan, and this collaboration led to the identification of an anti-VZV compound, i.e. the bicyclic furanopyrimidine derivative Cf 1743 (Cf standing for "Cardiff"), which was yet more potent (at subnanomolar concentrations) than BVDU (McGuigan et al., 2000; Andrei et al., 2005; De Clercq, 2003a). Inspired by the valine ester of acyclovir (valaciclovir), we also synthesized the 5′-O-valine ester of Cf 1743, and this compound, FV-100 (FV standing for "Fermavir"), has now progressed to phase II clinical trials for the treatment of herpes zoster (De Clercq, 2009a).

At the Göttingen meeting of 3–5 May 1976 I also encountered a Czech chemist (Czechoslovak at that time), I had never met before. He was rather suspicious, as he was (rightfully) wondering, no doubt, whether (and why) a medical doctor could (and even would) be interested in chemistry. This Czech chemist was Antonin Holý, and my first encounter with Dr. Holý on 3–5 May 1976 in Göttingen evolved to the highlight of my scientific life, with the discovery of an unprecedented number of specific antiviral agents, starting with DHPA (2,3-dihydroxypropyladenine) in 1978 (De Clercq et al., 1978), and followed by HPMPA (9-(3-hydroxy-2-phosphonylmethoxy-propyl)adenine) in 1986 (De Clercq et al., 1986), HPMPC (1-(3-hydroxy-2-phosphonylmethoxypropyl)cytosine) in 1987 (De Clercq et al., 1987), PMEA (9-(2-phosphonylmethoxyethyl)adenine) in 1986 (De Clercq et al., 1986), and PMPA (9-(3-phosphonylmethoxypropyl)adenine) in 1993 (Balzarini et al., 1993).

On 5 November 1986, Dr. Paul Janssen and I had a long conversation (lasting for at least 8 h) in Beerse (Belgium) where we decided to join our efforts [Dr. Paul's chemical library, and our expertise (built up by Rudi Pauwels in our Laboratory) in the evaluation of anti-HIV activity] to find a "cure" for AIDS. This collaboration led to the identification, through what I should describe as rational screening (i.e. selection of drug candidates followed by lead optimization) of the TIBO derivatives [the HEPT derivatives were discovered in parallel with the TIBO's (De Clercq, 2008)]. In retrospect, the HEPT's and TIBO's were the first non-nucleoside RT inhibitors (NNRTIs), a class of compounds that have gained a prominent position in the treatment of HIV infections, with four licensed compounds (nevirapine, delavirdine, efavirenz and etravirine) and a fifth one (rilpivirine), Dr. Paul's legacy, forthcoming (De Clercq, 2009b).

At several occasions in the late 1980s (15 December 1986, 2 November 1987, 4 November 1988) I met with Dr. John C. Martin, then Associate Director of Anti-Infective Chemistry of Bristol-Myers Company in Wallingford (Connecticut), to discuss the future of anti-HIV agents. John then asked what I thought should be the future option for treating HIV infections, NNRTIs or NRTIs (nucleoside RT inhibitors). [This was at a time the names NNRTIs and NRTIs were not yet invented.] So, what John meant, was whether I would go for nucleoside/nucleotide analogues such as azidothymidine (AZT) (known since 1985) and PMEA (known since 1986) or non-nucleoside analogues such as TIBO or HEPT [which had just been discovered in our Laboratory (1987, 1988)]. I remember I told him to consider both, the NNRTIs as gentle "frêles", hitting the virus gently (not being (very) toxic but rapidly leading to resistance), and the N(t)RTIs as powerful "sledge" hammers, hitting the virus vigorously (likely to have varying toxicity (depending on the compound) but not rapidly engendering resistance). These prophetic feelings, as I can judge today, have been largely borne out.

By the end of the 1980s the rights on the whole family of acyclic nucleoside phosphonates (discovered by Tony Holý and myself) were transferred (licensed) to Bristol-Myers, but, when John C. Martin, with the imminent merger of Bristol-Myers with Squibb, moved from Bristol-Myers to Gilead Sciences (in 1990), so did the acyclic nucleoside phosphonates, so that by 1991, Gilead Sciences had the full rights on these compounds, and, while originally conceived (in 1987) as an "antisense Company", with J.C. Martin as the driving force, and fuelled by Tony Holý's acyclic nucleoside phosphonates, Gilead Sciences rapidly became a "phosphonate Company".

Of the acyclic nucleoside phosphonates, HPMPC (cidofovir, Vistide®) was the first to be approved for clinical use, in 1996, for the treatment of cytomegalovirus (CMV) retinitis in AIDS patients; PMPA (tenofovir) was approved for clinical use, in its prodrug form, TDF (tenofovir disoproxil fumarate, Viread®) in 2001, for the treatment of AIDS; and PMEA was approved for clinical use, in its prodrug form, adefovir dipivoxil (Hepsera®) in 2002, for the treatment of chronic hepatitis B. Then followed, in 2004, the approval of the combination of TDF with emtricitabine (Truvada®), and in 2006, the approval of the combination of TDF with emtricitabine and efavirenz (Atripla®), both for the treatment of AIDS, and in 2008 the approval of Viread® for the treatment of hepatitis B. Forthcoming is the quadruple ("quad") drug combination existing of tenofovir

disoproxil fumarate (TDF), emtricitabine, elvitegravir (an integrase inhibitor) and GS-9350 (a "booster" or pharmacoenhancer, inhibiting the CYP 3A P450 enzyme, thereby "boosting" the blood levels of elvitegravir). This "quad" pill should, for TDF, constitute the fourth form in which it would be marketed.

A most important future strategy of TDF (Viread®), whether or not combined with emtricitabine (Truvada®), would lie in its prophylactic use to prevent HIV infections, irrespective of the route by which the virus is transmitted [parenterally (i.e. by needle stick), sexually (i.e. by vaginal intercourse) or perinatally (from mother to child)]. Prospects for HIV preexposure prophylaxis (PrEP) by Viread® or Truvada® in a preemptive strike against HIV, are particularly encouraging (Willyard, 2009; De Clercq, in press), especially if one takes into account that tenofovir and Truvada® can completely prevent SIV (simian immunodeficiency virus) infection in macaques (Tsai et al., 1995; Garcia-Lerma et al., 2008).

The year 1993, in retrospect, may have been a pivotal year in my career, not only because we for the first time then reported on PMPA (tenofovir) as being active against HIV (Balzarini et al., 1993), but, totally independently thereof, that same year I was contacted by a certain Eric Van Cutsem, later to become a famous gastroenterologist at our University, on how to treat a case of severe hypopharyngeal papillomatosis which had resisted all kinds of treatment (interferon, laser irradiation, surgery, etc.). I recommended to consider an (entirely new) approach, based on the compassionate use of a drug (cidofovir) which, only 3 years later (1996), would become licensed for clinical use (in the treatment of cytomegalovirus (CMV) retinitis in AIDS patients). This marked the launch of cidofovir in the (topical) treatment of human papillomavirus (HPV) infections (Van Cutsem et al., 1995), soon followed by the use of cidofovir for the (topical) treatment of other, i.e. laryngeal, HPV infections (Snoeck et al., 1998).

At present, five marketed products, Vistide®, Viread®, Hepsera®, Truvada® and Atripla®, eventually resulted from the interaction that started in May 1976 in Göttingen between two chemists (one real chemist: A. Holý, and one chemist at heart: myself). As in the "Holy Trinity" there should be a third, the Holy Spirit, in this case, John C. Martin, currently Chief Executive Officer (CEO) and President of Gilead Sciences, who, being a chemist himself, brought the acyclic nucleoside phosphonates, adefovir, cidofovir, and tenofovir, to the reach and the benefit of mankind, worldwide. The Holy Trinity, as represented by Tony Holý, myself and John C. Martin, should also serve as a paradigm for the successful development of antiviral drugs, the interplay between three disciplines: chemistry, biology/medicine and industry. As I mentioned before (De Clercq, 2009a) "crucial factors being open mindedness for the unexpected, preparedness to explore serendipitous observations, and perseverance (in trying) to overcome the hurdles or setbacks inevitably compounding any drug development".

Speaking of serendipity, the bicyclams, i.e. AMD3100 (AMD standing for "AnorMED"), should be mentioned. The original bicyclam AMD1657 or then named JM1657 (JM standing for "Johnson Matthey") was identified as an impurity in a commercial monocyclam preparation, when we were evaluating cyclams for their potential anti-HIV activity (De Clercq et al., 1992). Synthesis of derivatives of AMD1657 then led to the identification of AMD2763 and AMD3100, the latter being inhibitory to HIV replication in the nanomolar concentration range (De Clercq, 2003b). Its mechanism of anti-HIV action was resolved as resulting from its antagonization with the HIV coreceptor CXCR4 (Schols et al., 1997a,b; Donzella et al., 1998). As a CXCR4 antagonist, AMD3100 was then found to counteract the "homing" of hematopoietic stem cells and hence to mobilize these cells from the bone marrow; and AMD3100, albeit initially discovered as an anti-HIV agent, has now, since December 2008, been officially licensed as a stem cell mobilizer (under the trade name Mozobil™), i.e. for autologous stem cell transplantation in patients with Non-Hodgkin's Lymphoma (NHL) or Multiple Myeloma (MM) (De Clercq, 2009c).

Looking back to the past, and considering the present and looking forward to the future, there have been a few milestones in my life. My career actually started in 1946, when my father, a chemist, introduced me, when I was 5 years old, to the smell of chemistry (at that time sulfuric acid in the plant of fertilizers where he worked). Another milestone was 1959, when I entered the Medical Faculty at our University (why Medicine?, simply because they had such a comprehensive course on chemistry in the first year of the medical studies). In 1966 I graduated as MD from the Leuven University Medical School. In 1976, I would meet Dr. A. Holý for the first time, and in 1986, we described the first acyclic nucleoside phosphonates HPMPA and PMEA. 1986 has been the year when Dr. Paul Janssen and I sat together and decided to combine our efforts to (try to) develop a "cure" for AIDS. Further milestones have been 1996, when cidofovir was licensed for the treatment of CMV infections in AIDS patients, 2001, when tenofovir disoproxil fumarate (Viread®) was licensed for the treatment of HIV infections (AIDS); 2002, when adefovir dipivoxil (Hepsera®) was licensed for the treatment of HBV infections (hepatitis B); 2004 and 2006, when Truvada® and Atripla®, respectively, were launched for the treatment of HIV infections (De Clercq and Holý, 2005; De Clercq, 2006, 2007a,b); and 2008, when Viread® was formally approved for the treatment of hepatitis B (De Clercq, 2009b).

In summary, AZT (azidothymidine) heralded the advent of many more agents targeted at the reverse transcriptase (RNA-dependent DNA polymerase) as the key enzyme in the replicative cycle of HIV. The RT would emerge as the target for both nucleoside RT inhibitors (NRTIs) and nucleotide RT inhibitors (NtRTIs) as well as non-nucleoside RT inhibitors (NNRTIs) (with rilpivirine as likely the fifth NNRTI to be licensed for clinical use). Independently from, and actually preceding, AZT and the other 2′,3′-dideoxynucleoside analogues, were the selective anti-HSV and -VZV agents acyclovir and BVDU, both targeted at the DNA polymerase involved in the replication of herpesviruses (HSV and VZV). For the NtRTIs adefovir and tenofovir the activity spectrum was found to extend to hepadnaviruses [hepatitis B virus (HBV)] which for their replication rely on an RNA-dependent DNA polymerase similar to that of the HIV reverse transcriptase.

As an epilogue, the successful development of antiretroviral drugs as described here in more detail for the acyclic nucleoside phosphonates but actually valid for the anti(retro)virals in general critically depends on the interplay between three different disciplines: chemistry, biomedicine and industry. This interplay is of crucial importance in conceiving the compound, validating its biomedical usefulness, and successfully developing it for clinical use.

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