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The Acyclic Nucleoside Phosphonates (ANPs): Antonín Holý's Legacy (2012 – 2018)

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Antonín Holý died on 16 July 2012 (obituary[1a,1b]). Precisely that day the US Food and Drug Administration (FDA) approved Truvada®, the combination of TDF (tenofovir disoproxil fumarate) with emtricitabine, for the prophylaxis of HIV infections [on 22 August 2016 Truvada® was also approved in the EU for the prophylaxis of HIV infections]. Truvada® had been approved in 2004 for the treatment of HIV infections, but it turned out to be the only chemical compound ever formally approved for the prevention of HIV infections, now commonly referred to as PrEP (Pre-Exposure Prophylaxis). Now that Truvada® has been replaced by Descovy® [combination of tenofovir alafenamide (TAF) with emtricitabine] for the treatment of HIV infections, Descovy® may eventually be considered to substitute for Truvada® in the prevention of HIV infections, after it has been proven efficacious for PrEP.

With the discovery of adefovir (prodrug adefovir dipivoxil, Hepsera®), cidofovir and tenofovir, Holý laid the basis for the use of the acyclic nucleoside phosphonates (ANPs) in the chemotherapy of virus infections. Metal-binding properties of the ANPs represent another part of the legacy of Dr. Holý[2,3]. Since it was approved in 2001, TDF (Viread®) has been one of the cornerstones in the treatment of HIV infections. Following Truvada® in 2004, the combination of TDF with emtricitabine and efavirenz (Atripla®) was approved in 2006, the combination of TDF with emtricitabine and rilpivirine (Complera® in the US, Eviplera® in the EU) was approved in 2011, and the quadruple combination of TDF with emtricitabine, elvitegravir and cobicistat (Stribild®) was approved in 2012, all combinations intended for the treatment of HIV infections.

As TDF ran out of patent protection in 2017, it has since then been replaced by another prodrug of tenofovir, Tenofovir alafenamide (TAF)(GS 7340)[4] (Figure 1). TAF was approved by the US FDA as such (Vemlidy®) in 2016, in combination with emtricitabine, elvitegravir and cobicistat (Genvoya®) in 2015, in combination with emtricitabine and rilpivirine (Odefsey®) in 2016, and in combination with emtricitabine and bictegravir (Biktarvy®) in 2018. The latter drug containing the integrase inhibitor, bictegravir, may well represent the "ideal" treatment for HIV infections as it unites high efficiency, high tolerability with the lack of resistance development, at least through a period of 48 weeks[5].

Viread® and Vemlidy® were also approved by the US FDA in 2008 and 2017, respectively, for the treatment of hepatitis B virus (HBV) infections. While for the treatment of HIV infections the standard of care generally requires several drug combinations (i.e., containing

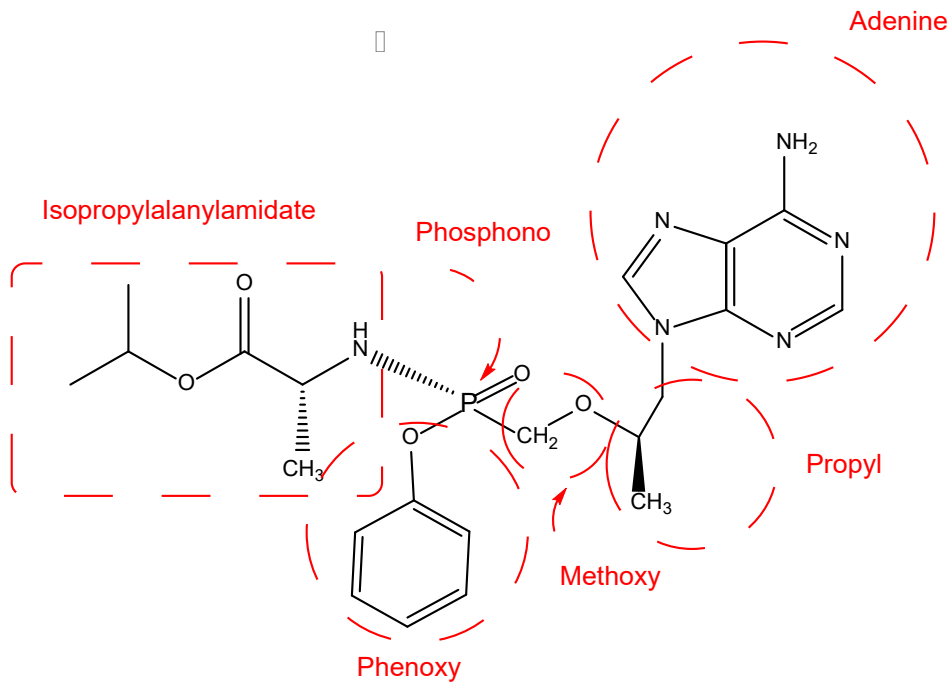

Figure 1: TAF (Tenofovir alafenamide)
Alafenamide (phenoxy isopropylalanineamidate), prodrug of tenofovir (R)-PMPA, PMPA standing for 9-(2-phosphonomethoxypropyl) adenine

previously TDF and nowadays TAF), the treatment of HBV infections routinely exists of a single compound (daily).

In 2017, the US FDA approved Tanovea® (rabacfosadine, VDC-1101) for the treatment of lymphoma in dogs[6]. This compound also represents part of the legacy of Antonín Holý. It could be considered as a pro-prodrug of PMEG, which we first described in 1987 as a member of the ANPs[7]. However, the compound was not further pursued as a potential antiviral drug, because of its cytotoxicity. Its prodrug however, cPr-PMEDAP [9-(2-phosphonylmethoxyethyl)-N^6-cyclopropyl-2,6-diaminopurine] was found to be effective in rats as an antitumor agent, i.e., against choriocarcinoma[8]. Following this lead, GS-9219, a prodrug of this compound, was specifically targeted at the lymphatic tissue, and was found to specifically inhibit Non-Hodgkin's lymphoma (NHL) in dogs[9]. GS-9219 was then sublicensed by Gilead Sciences to Vet DC and finally registered for veterinary use against lymphoma in dogs.

While cidofovir [(S)-HPMPC, (S)-1-(3-hydroxy-2-phosphonylmethoxy)propyl 1-cytosine] was originally approved for the treatment of human cytomegalovirus (HCMV) retinitis in AIDS patients, a severe complication leading to blindness, that is virtually no longer observed with the improved therapeutic regimens for the treatment of AIDS, cidofovir has been used off label for the treatment of various other DNA virus infections, including herpes simplex, adeno-, pox (monkeypox, orf, molluscum contagiosum), papilloma (genital warts, larynx papilloma, respiratory papillomatosis) and polyomavirus infections, and these indications should be revisited in more rigorously conducted clinical trials. Especially for poxvirus infections, for which as of today, no specific treatment has been established [except for tecovirimat (previously ST-246)[10]], cidofovir still offers a unique opportunity: it has proven highly efficacious in a murine model of disseminated progressive vaccinia[11], and it is clearly more effective than smallpox vaccination against a lethal monkey poxvirus infection[12].

Also belonging to Antonín Holý's legacy are the 6-[2-(phosphonomethoxy)alkoxy] pyrimidines, with (R)-HPMPO-DAPy, PMEO-DAPy and (R)-PMPO-DAPy as the prototypes[13,14]. The former compound has an activity spectrum similar to that of (S)-HPMPC, whereas the latter two may be similar to that of PMEA (adefovir) and (R)-PMPA (tenofovir). Their true antiviral potential still remains unresolved[15].

Equally uncertain remains the therapeutic potential of (S)-HPMP-5-azaC, cyclic (S)-HPMP-5-azaC and their alkoxyalkyl prodrugs[16,17]. Also, these 5-azaC (or triazine) analogues of (S)-HPMPC and their lipid conjugates (akin to brincidifovir) should deserve further attention, and so should be the potential of ANPs in the elimination of plant viruses, such as that of banana streak virus by adefovir and tenofovir[18].

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