BIOCHEMICAL PHARMACOLOGY 73 (2007) 911–922

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Commentary

Acyclic nucleoside phosphonates: Past, present and future Bridging chemistry to HIV, HBV, HCV, HPV, adeno-, herpes-, and poxvirus infections: The phosphonate bridge

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ARTICLE INFO

Keywords:
Acyclic nucleoside phosphonates
Nucleotide analogues
Cidofovir
Adefovir
Tenofovir
Antiviral activity

ABSTRACT

Twenty years following the description of the broad-spectrum antiviral activity of S-9-(3-hydroxy-2-phosphonylmethoxypropyl)adenine [(S)-HPMPA] [De Clercq E, Holý A, Rosenberg I, Sakuma T, Balzarini J, Maudgal PC. A novel selective broad-spectrum anti-DNA virus agent. Nature 1986;323:464–7], the acyclic nucleoside phosphonates have acquired a prominent therapeutic position: (i) cidofovir in the treatment of papilloma-, herpes-, adeno- and poxvirus infections, (ii) adefovir in the treatment of chronic hepatitis B virus (HBV) infections, and (iii) tenofovir in the treatment of human immunodeficiency virus (HIV) infections (AIDS). Although formally approved only for the treatment of human cytomegalovirus (HCMV) retinitis in AIDS patients, cidofovir has been used successfully in the treatment of various other DNA virus infections, particularly human papilloma virus (HPV)-associated lesions. Adefovir dipivoxil has become a standard therapy for HBV infections, especially when resistant to lamivudine. Tenofovir disoproxil fumarate (TDF) is the corner stone of the triple-drug (TDF, emtricitabine, and efavirenz) combination therapy for AIDS, and TDF, alone or combined with emtricitabine may in the future evolve to the standard therapy of hepatitis B. Guided by the results obtained with tenofovir in the prevention of parenteral, intravaginal and perinatal infections with simian immunodeficiency virus in monkeys, and the safety profile gathered with TDF in humans with AIDS over the past 5 years since TDF was licensed for clinical use, it should be further pursued for the pre- and post-exposure prophylaxis of HIV infections in humans. Meanwhile, new classes of both acyclic (i.e. PMPO-DAPy, PMEO-DAPy, HPMPO-DAPy) and cyclic nucleoside phosphonates (i.e. PMDTA, PMDTT, GS9148) have been accredited with an antiviral potency and selectivity similar to those of cidofovir, adefovir and/or tenofovir.

1. Introduction

The story that would eventually lead to the successful commercialization of the acyclic nucleoside phosphonates as antiviral drugs started some 30 years ago. I met then with Dr. Anthonin Holý at a Symposium (organized by the late Karl-Heinz Scheit) on Synthetic Nucleosides, Nucleotides and Polynucleotides at the Max-Planck-Institut für Biophysikalische Chemie in Göttingen, Germany, on 3–6 May 1976. We decided to collaborate on the exploration of the antiviral activity of new nucleoside analogues, in particular acyclic nucleoside analogues, and the first compound we found active

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doi:10.1016/j.bcp.2006.09.014

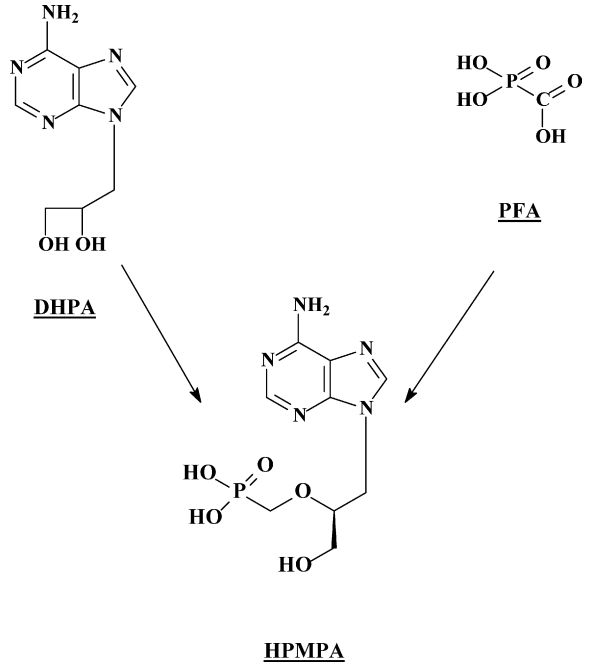


Fig. 1 – (S)-9-(3-Hydroxy-2-phosphonylmethoxypropyl)adenine (HPMPA), and its predecessors 9-(2,3-dihydroxypropyl)adenine (DHPA) and phosphonoformic acid (PFA).

in this series was DHPA [9-(2,3-dihydroxypropyl)adenine] [2]. This publication came just a few months after the acyclic guanosine analogue acyclovir had been described as a selective anti-herpes simplex virus (HSV) agent [3] that owed its selectivity to a specific phosphorylation by the HSV-induced thymidine kinase (TK) [4]. Although less potent than acyclovir against HSV, DHPA was active against a broad range of both DNA and RNA viruses, and its antiviral effects, as shown later were due to interference with the S-adenosylhomocysteine (SAH) hydrolase, thus inhibiting viral RNA maturation. In the early eighties, we examined the antiviral potential of various other acyclic nucleoside analogues, i.e. AHPA derivatives [5]. Their antiviral activity spectrum was essentially similar to that of DHPA and so was their mechanism of action.

With (S)-9-(3-hydroxy-2-phosphonylmethoxypropyl)adenine (HPMPA) a totally new concept was born [1]. This acyclic nucleoside phosphonate, which could be envisaged as an hybrid molecule between DHPA and PFA (phosphonoformic acid) (Fig. 1) exhibited a remarkable broad-spectrum activity against virtually all DNA viruses, including those that did not induce a specific viral TK, such as human cytomegalovirus (HCMV), or had become resistant to acyclovir by a deficiency in their TK, such as the TK^- HSV strains. Although HPMPA itself was not further developed as an antiviral drug, it served as the prototype compound for a series of acyclic nucleoside phosphonates (cidofovir, adefovir and tenofovir), which would ultimately be approved for clinical use (in 1996, 2002 and 2001, respectively).

2. Cidofovir

The antiviral properties of (S)-1-(3-hydroxy-2-phosphonylmethoxypropyl)cytosine (HPMPC, cidofovir), now on the market as Vistide® (Fig. 2) were first described in 1987 [6]. The antiviral activity spectrum of cidofovir (HPMPC) is similar to that of HPMPA. It is active against virtually all DNA viruses, including polyoma-, papilloma-, adeno-, herpes-, and poxviruses. Among the family of herpesviridae, all eight human herpesviruses (HSV-1, HSV-2, VZV, EBV, HCMV, HHV-6, HHV-7 and HHV-8), and, among the poxviruses, vaccinia, variola, cowpox, monkeypox, camelpox, molluscum contagiosum and orf, have proved to be susceptible to the inhibitory effects of cidofovir. Its mechanism of action, as in the case of HCMV, has been clearly demonstrated (Fig. 3); it is based on DNA chain termination (following the intracellular conversion of cidofovir to its diphosphate and the successive incorporation of two cidofovir units into the growing DNA chain [7].

From a clinical viewpoint, cidofovir has been licensed for use, upon intravenous administration at a dose of 5 mg/kg once every other week, in the treatment of HCMV retinitis in AIDS patients (for key clinical data, see Ref. [8]). Its future, however, lies in the remarkable, albeit anecdotal, results

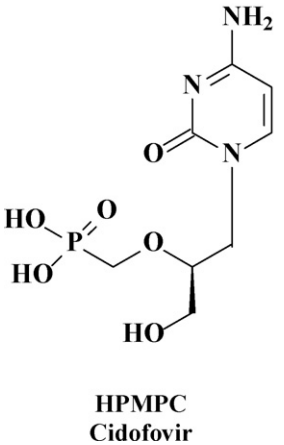


Fig. 2 – (S)-1-(3-Hydroxy-2-phosphonylmethoxypropyl)cytosine (HPMPC, cidofovir, Vistide®).

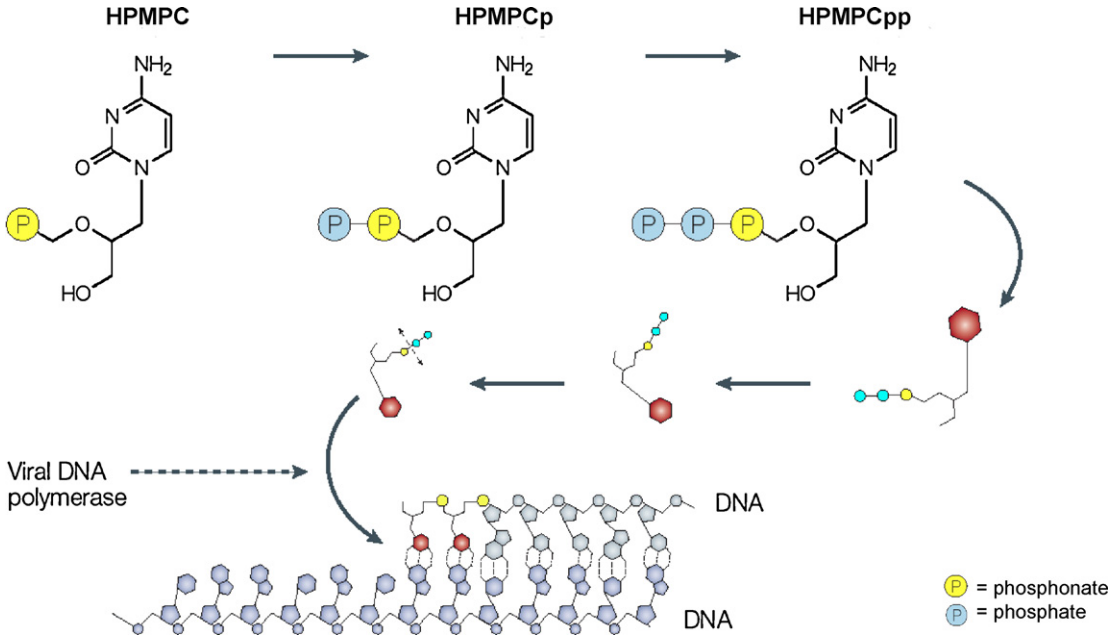


Fig. 3 – Mechanism of action of cidofovir (taken from Ref. [7]).

which have been accumulated with cidofovir when used topically or systemically in the treatment of HPV-associated diseases such as hypopharyngeal papilloma [9], laryngeal papilloma [10], recurrent respiratory papillomatosis [11] or plantar warts [12], or poxvirus-associated diseases, such as molluscum contagiosum in AIDS patients [13] or orf (ecthyma contagiosum) in immunosuppressed patients [14]. Clearly, cidofovir should be further pursued for its potential in the treatment of those virus infections (i.e. papilloma, pox) for which, at present, there are few, if any, therapeutic alternatives.

3. Adefovir

The antiviral activity of 9-(2-phosphonylmethoxyethyl)adenine (PMEA, adefovir, now marketed as its oral prodrug form [bis(pivaloyloxy methyl) ester of PMEA, adefovir dipivoxil, Hepsera®] (Fig. 4) was first mentioned in the paper [1] describing the antiviral properties of HPMPA. The antiviral activity spectrum of adefovir is partially overlapping with that of cidofovir in that both are active against herpesviruses (i.e. HSV-1, HSV-2, VZV, EBV, HCMV), but, in addition, adefovir is also active against hepadnaviruses (i.e. human and duck hepatitis B viruses) and retroviruses (HIV-1, HIV-2, SIV, feline immunodeficiency virus (FIV), visna/maedi virus, feline leukemia virus, LP-BM5 (murine AIDS) virus and Moloney (murine) sarcoma virus).

In its mechanism of action (Fig. 5), adefovir follows a similar strategy as cidofovir. Once adefovir has penetrated into the cell, it needs two subsequent phosphorylations to be converted to its diphosphate, which, after removal of the pyrophosphate moiety, is incorporated into the viral DNA and acts as an obligatory DNA chain terminator [7].

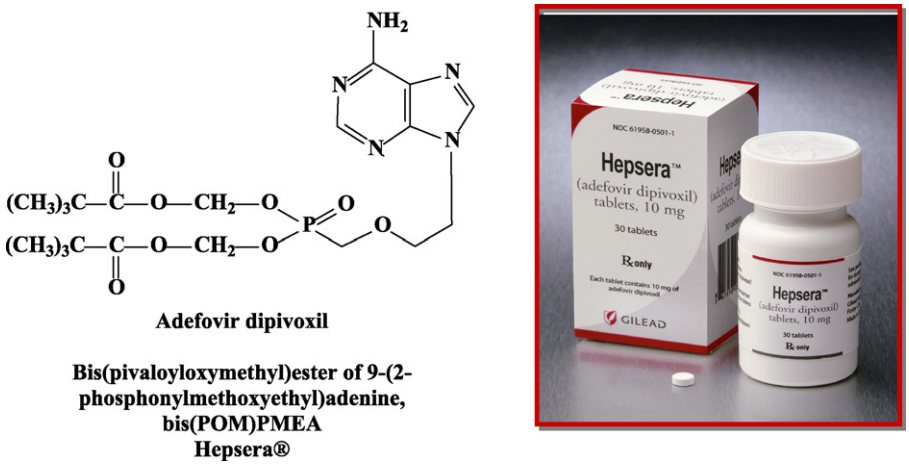


Fig. 4 – Adefovir dipivoxil (Hepsera®).

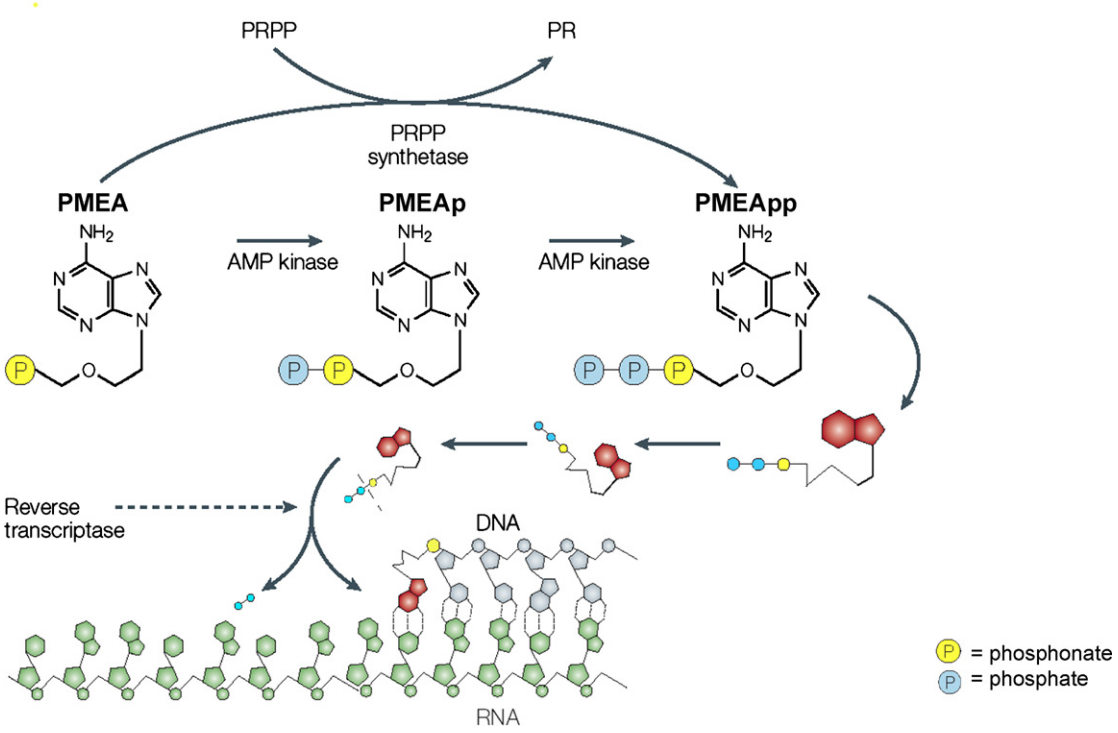


Fig. 5 – Mechanism of action of adefovir (taken from Ref. [7]).

From a clinical viewpoint, adefovir was first pursued for its potential use in the treatment of HIV infections (AIDS) but was eventually licensed in its prodrug form (adefovir dipivoxil) for the treatment of HBV infections (chronic hepatitis B) [8]. Even when used at a dose of as low as 10 mg/day, adefovir dipivoxil was found to bring down the HBV DNA viral loads by several orders of magnitude. The benefits achieved with adefovir dipivoxil over a 48-week treatment period in patients with (either HBeAg-positive or -negative) chronic hepatitis B [15,16] were maintained if treatment was extended to 144 weeks (in HBeAg-negative chronic hepatitis B) [17]. Fig. 6 illustrates three points: (i) persistence of the antiviral efficacy (monitored by serum HBV DNA levels) through 96 weeks of treatment, (ii) loss of antiviral efficacy if treatment was discontinued after the initial 48 weeks, and (iii) (re)gain of antiviral efficacy if treatment was installed for the second 48-week period [17].

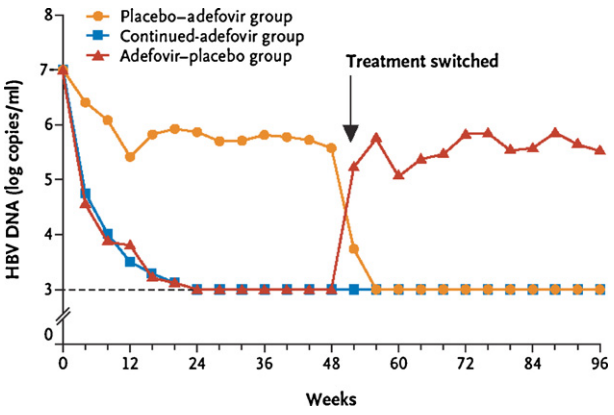


Fig. 6 – Long-term therapy with adefovir dipivoxil for HBeAg-negative chronic hepatitis B. Median serum HBV DNA levels through week 96. Lower limit of detection was 3 log copies per milliliter (taken from Ref. [17]).

In a large clinical study on the efficacy of adefovir as a treatment for chronic hepatitis B, the rt N236T or rt A181V mutation developed in 5.9% of the patients within 3 years. The *in vitro* efficacy [17] against these adefovir-induced mutants decreased by 2.5- to 13.8-fold. Recently, three cases of primary adefovir resistance were described [18]. All three cases involved a rare HBV variant with a valine at position 233 of the reverse transcriptase domain instead of isoleucine (rt I233V). This rt I233V mutation decreased the *in vitro* efficacy of adefovir by a factor of 6–10 and was already present before adefovir therapy was initiated [18].

4. Tenofovir

4.1. *Therapeutic use of tenofovir*

The antiviral activity of (*R*)-9-(2-phosphonylmethoxypropyl)adenine (PMPA, tenofovir, now marketed as its oral prodrug form [bis(isopropyloxycarbonyloxymethyl) ester of PMPA, tenofovir disoproxil fumarate, TDF, Viread®] (Fig. 7) was first described in 1993 [19] in a paper also pertaining to the activity of its 2,6-diaminopurine counterpart. The anti-HIV effects of the (*R*)-enantiomers of PMPA and PMPDAP were demonstrated in several human cell systems, including peripheral blood lymphocytes and freshly isolated monocyte-macrophages [20]. The *in vivo* anti-HIV efficacy of the prodrug, bis(isopropyloxycarbonyloxymethyl)-(*R*)-9-(2-phosphonylmethoxypro-

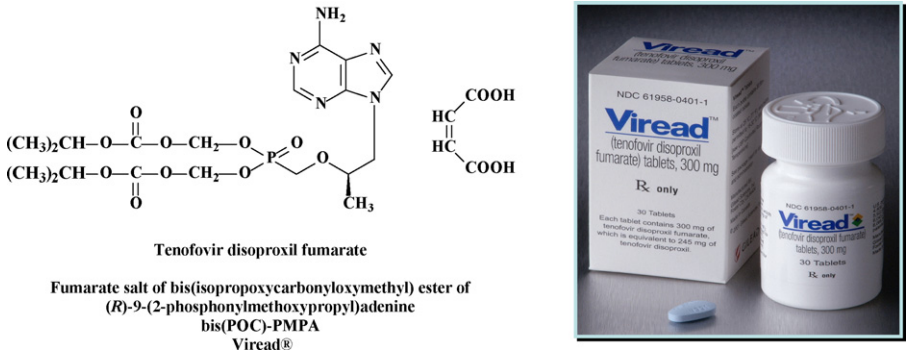


Fig. 7 – Tenofovir disoproxil fumarate (TDF, Viread®).

pyl)adenine, and its cellular metabolism were reported by Naesens et al. [21] and Robbins et al. [22].

The antiviral activity spectrum of tenofovir is narrower than that of adefovir, in that it no longer extends to herpesviruses but is confined to hepadna- and retroviruses. In its mechanism of action, tenofovir is assumed to follow exactly the same strategy as that of adefovir [23].

From a clinical viewpoint, tenofovir disoproxil fumarate (TDF) has been licensed for the treatment of HIV infections (AIDS), as either a single drug (Viread®) (Fig. 7) once daily, or in combination with emtricitabine (Truvada®) (Fig. 8) as one pill daily, or, most recently, in combination with emtricitabine and efavirenz (Atripla™) (Fig. 9), again as one pill daily. The latter can be considered a true breakthrough in the clinical management of HIV infections, as it represents the first HAART (highly active antiretroviral therapy) cocktail administered as a single tablet once daily. This is a long way from the twenty some pills a day that HAART was based upon a decade ago. The single tablet regimen containing three preferred antiretrovirals will undoubtedly simplify the treatment of HIV infections and substantially improve patient compliance.

Why would tenofovir disoproxil fumarate (TDF), emtricitabine and efavirenz qualify as preferred antiretrovirals to be combined in a single tablet for HIV therapy? Indicative for this choice were the results of Study GS 934 comparing the clinical and virological efficacy, and safety of TDF, emtricitabine and efavirenz *versus* zidovudine, lamivudine and efavirenz [24]. This study revealed that through week 48, the combination of TDF and emtricitabine plus efavirenz (all three once-daily) fulfilled the criteria for noninferiority to a fixed dose of zidovudine and lamivudine (combivir, twice-daily) plus efavirenz (once-daily), and proved superior in terms of virologic suppression, CD4 response, and adverse events leading to discontinuation of the study drugs [24]. At week 48, the proportion of patients with HIV RNA levels below 400 copies per ml (the so-called ''responders'') was 73% in the zidovudine/lamivudine arm *versus* 84% in the TDF/emtricitabine arm ($p = 0.002$) (Fig. 10). Thus, taking into account the different criteria (efficacy, safety and ease of administration) the combination of TDF, emtricitabine and efavirenz proved to be superior to the combination of zidovudine, lamivudine and efavirenz.

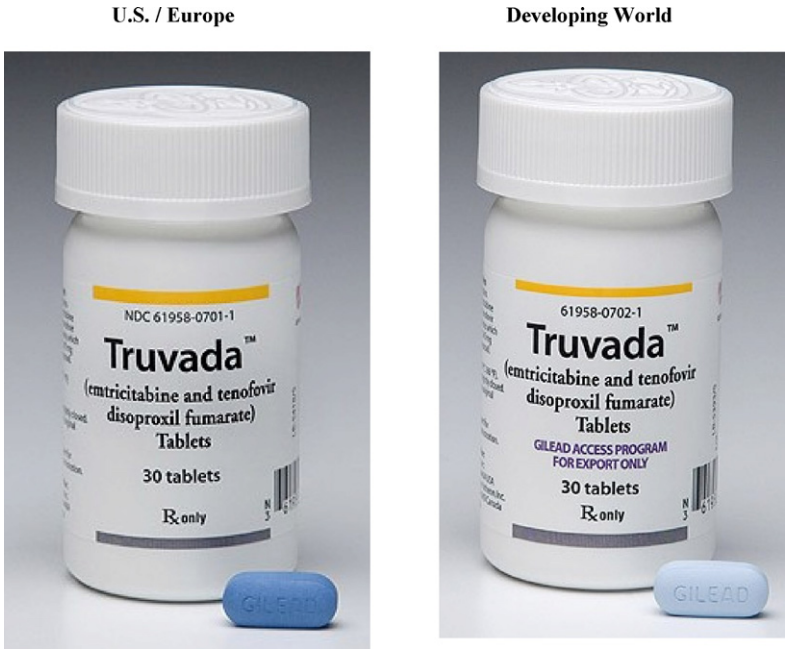


Fig. 8 – Truvada™: combination of emtricitabine with tenofovir disoproxil fumarate.

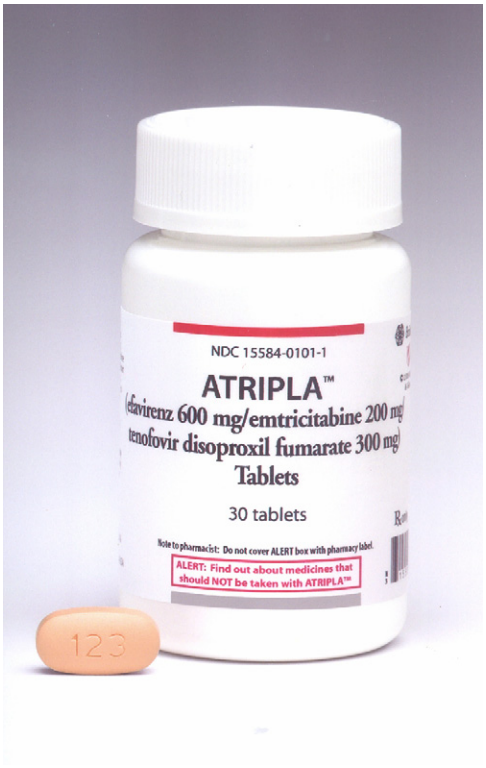


Fig. 9 – Atripla™: combination of Truvada (see Fig. 8) with Efavirenz (Sustiva™).

The most feared adverse event of acyclic nucleoside phosphonates, i.e. tenofovir, is renal tubular dysfunction, acute renal failure or Fanconi syndrome; these complications have been noted particularly in AIDS patients with underlying kidney conditions or taking concomitantly other potential nephrotoxic agents [25,26]. However, renal dysfunction did not occur more frequently with TDF than with other antiretroviral drugs, and, when it occurred, it was usually attributable to other causes [27].

There may be a modest decline in renal function in TDF-treated patients with prolonged TDF use, especially in patients with advanced HIV disease, diabetes, or a decreased renal function at base line. The clinical significance of these findings [28] has remained unclear, but has not been perceived as a reason to withhold TDF treatment from patients who would benefit from it. Several studies in HIV drug treatment-experienced patients indicated that through 24 weeks [29], or 48 weeks [30], TDF achieved a significant reduction in HIV-1 RNA levels, while exhibiting a safety profile similar to that of placebo. The incidence of renal dysfunction was similar among the TDF and placebo groups in two double-blind, placebo-controlled studies [31].

The signature resistance mutation for TDF is the HIV reverse transcriptase mutation K65R [32]. This mutation causes a variable (but not complete) loss in susceptibility to tenofovir and other anti-HIV compounds such as didanosine and abacavir. Typically, the K65R mutation leads to only a three- to four-fold reduction in tenofovir susceptibility, and was detected in only 3% of the patients on TDF treatment [33]. From *in vitro* phenotypic analysis, the K65R mutation shows no cross-resistance to zidovudine, and for patients who developed the K65R mutation in clinical trials, successful second-line regimens have been established [34]. Furthermore, as described *infra* (Section 4.2), HIV strains harboring the K65R mutation show diminished replicative fitness.

4.2. *Prophylactic use of tenofovir*

Three key observations point to the efficacy of tenofovir in the prevention of retrovirus infections. First, Tsai et al. [35] reported that tenofovir, when administered subcutaneously once daily beginning either 48 h before, 4 h after or 24 h after virus inoculation, and continued for 4 weeks, completely protected macaques against intravenous SIV infection. Second, Otten et al. [36] reported that tenofovir when administered subcutaneously at 30 mg/kg for 28 days starting at 12 or 36 h after intravaginal infection of macaques with HIV-2, completely prevented the HIV infection. Third, Van Rompay et al. [37] reported that tenofovir, when administered

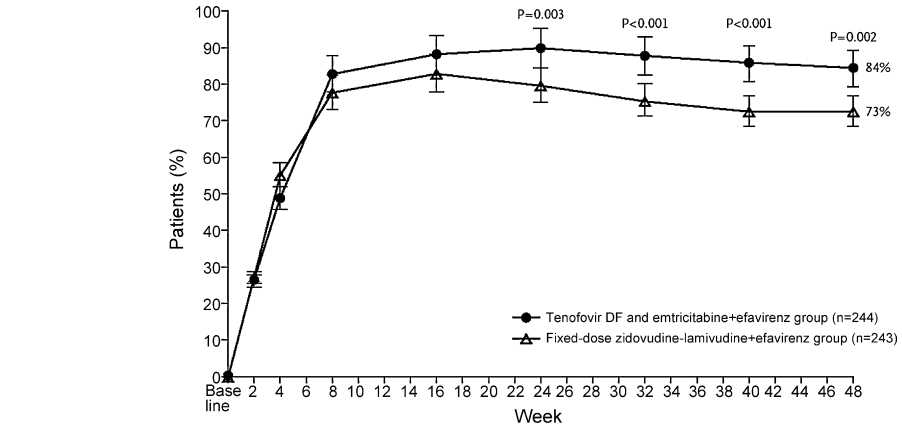


Fig. 10 – Proportion of patients with HIV RNA levels below 400 copies/ml: Viread–Emtriva–Sustiva *vs.* Combivir–Sustiva (taken from Ref. [24]).

subcutaneously at 2 doses of 4 mg/kg either 4 h before or 20 h after, or 1 and 25 h after, or as a single dose of 30 mg/kg at 1 h after SIV inoculation in newborn macaques inoculated orally with SIV at the age of 3 days, completely protected the monkeys against perinatal SIV infection.

While oral TDF (tenofovir disoproxil fumarate) delayed, but ultimately did not prevent, infection with SHIV (simian human immunodeficiency virus) in rhesus macaques repeatedly given rectal challenges with SHIV [38], combination of tenofovir with emtricitabine, both administered subcutaneously, completely prevented rectal SHIV transmission in macaques [39].

Based on these experimental studies pertaining to the efficacy of systemically administered tenofovir (whether or not combined with emtricitabine) in the prevention of parenteral, intravaginal or perinatal retrovirus infections, combined with the safety/efficacy profile that has been established for tenofovir disoproxil fumarate (TDF) in the treatment of AIDS in humans over the past 5 years (2001–2006) since TDF was approved for clinical use, TDF could be strongly recommended (as a single daily pill) in the pre- and post-exposure prophylaxis of HIV infections in humans.

Apart from the potential application of tenofovir vaginal gel as a microbicidal formulation [40], indications for the prophylactic use of systemic tenofovir (that is TDF by the oral route) would be (i) parenteral HIV inoculation (i.e. needle stick accident), (ii) sexual HIV transmission (by either the vaginal, anal or oral route) and (iii) perinatal HIV infection (before, during or after birth).

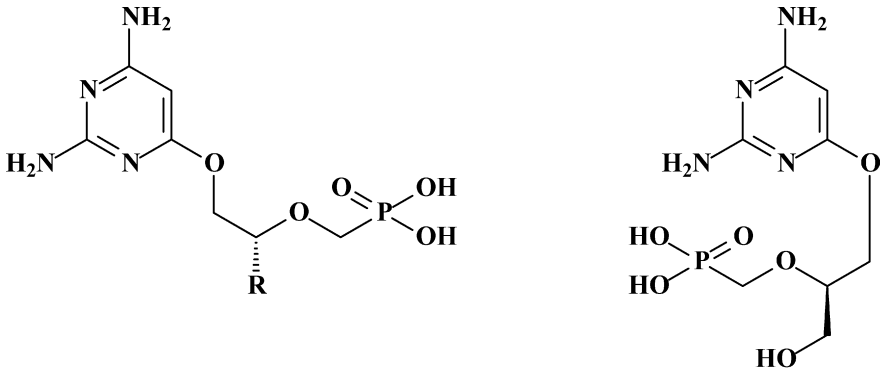
Theoretical concerns against the wide-scale prophylactic use of TDF to prevent HIV infections include (i) risk for toxicity on the long term, (ii) emergence of virus-drug resistance and (iii) stimulation of promiscuity. Counteracting these concerns, however, are the following: first, TDF has proven to be relatively free of side effects (i.e. kidney toxicity, bone demineralization), as witnessed over the 5-year follow-up period that the compound has been given to AIDS patients who may seem more prone to the potential adverse effects of TDF than healthy individuals. Second, emergence of HIV resistance to TDF has not proven to be a significant problem in HIV-infected individuals, where there is a continuous exposure of the virus to the compound. In fact, the tenofovir-related resistance RT (reverse transcriptase) mutation (K65R) [41] seems to disappear in time, in favor of the K70E mutation [42], which leads to lesser resistance; and this may be related to the reduced replicative fitness of the K65R mutant [43]. If the resistance K65R mutation is not a problem in AIDS patients, it is unlikely to be a problem in non-HIV infected individuals where exposure to HIV, if it occurs, will only be discontinuous. Third, the fear that the wide-scale use of TDF might stimulate promiscuity in the sense of increases in homo- or heterosexual contacts or parenteral drug abuse should by no means detract from the protection offered by TDF in preventing unwanted HIV infections in individuals who are unwillingly exposed to them.

4.3. *Tenofovir against HBV*

At present, adefovir dipivoxil is used for the treatment of HBV infections, and particularly recommended when HBV has developed resistance to lamivudine, whereas tenofovir (disoproxil fumarate) is recommended for use in the treatment of HIV and HIV/HBV co-infections. In this respect, a retrospective analysis has demonstrated the efficacy of TDF against both wild-type and lamivudine-resistant HBV when used as part of antiretroviral therapy in HIV/HBV-coinfected patients [44].

In terms of its *in vitro* intrinsic potency against HBV (whether wild-type or lamivudine-resistant), tenofovir is equipotent to adefovir (see, for example [45]), and, as it is administered (orally) at an approximately 30-fold higher dose (300 mg *versus* 10 mg), TDF may achieve higher *in vivo* efficacy against HBV than adefovir dipivoxil. Both TDF and adefovir dipivoxil proved to be efficacious and safe in the treatment of HBV infections in subjects co-infected with HIV [46]. In addition to therapeutic use, TDF (whether or not in combination with emtricitabine) may also be entertained for prophylactic use against HBV infections, which are transmitted by essentially the same routes (i.e. parenteral, sexual and perinatal) as HIV infections.

Given the activity of tenofovir against lamivudine-resistant (L180M + M204V/I) HBV mutants [45], and the fact that the major adefovir resistance mutation (N236T) confers only three- to four-fold reduced susceptibility to tenofovir in cell culture (the clinical significance of which remains to be



R = CH_3 : PMPO-DAPy

R = H: PMEO-DAPy

HPMPO-DAPy

Fig. 11 – PMPO-DAPy, PMEO-DAPy and HPMPO-DAPy (see Ref. [49]).

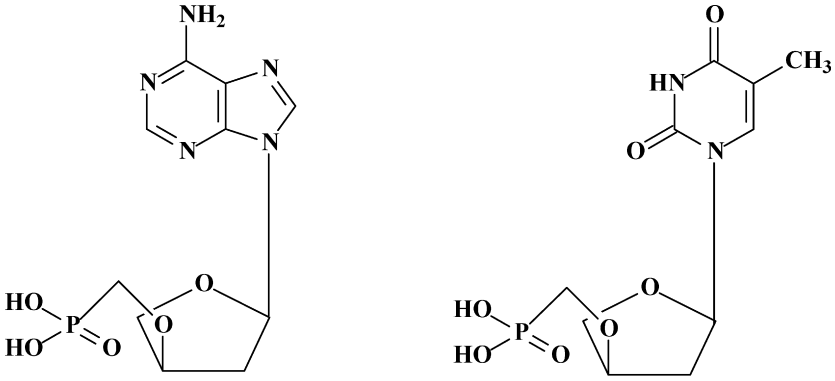


Fig. 12 – PMDTA and PMDTT (see Ref. [52]).

determined), the overall antiviral and metabolic profile of tenofovir supports its development for the treatment of HBV infections [47].

Recently, three cases of primary adefovir resistance were described which remained sensitive to tenofovir. The HBV variant involved had the I233V mutation at the RT domain [18]. *In vivo*, the HBV infection (as monitored by HBV DNA viremia) responded to tenofovir, but not adefovir. Also, *in vitro* the I233V variant displayed resistance to adefovir while retaining sensitivity to tenofovir [18].

Thus, tenofovir (disoproxil fumarate) holds great promise for the therapy (and prophylaxis) of HBV infections, also because it may be expected to be active against mutations engendering resistance towards lamivudine and partial to full cross-resistance towards entecavir, emtricitabine, clevudine and telbivudine [45]. Recently, a novel mutation, rT A194T, was described that reduced susceptibility of HBV to TDF in the presence of lamivudine-associated resistance mutations [48].

5. New acyclic nucleoside phosphonates

In recent years we have described new acyclic nucleoside phosphonates, the so-called 2,4-diaminopyrimidine (DAPy) derivatives (Fig. 11), in which the pyrimidine ring has been linked, through an oxygen bridge, to either the 2-phosphonylmethoxyethyl or 2-phosphonylmethoxypropyl entity, as in PMEO-DAPy and (*R*)-PMPO-DAPy, or the 3-hydroxy-2-phosphonylmethoxypropyl entity, as in (*S*)-HPMPO-DAPy. PMEO-DAPy, (*R*)-PMPO-DAPy. 5-Substituted PMEO-DAPy derivatives have proven particularly effective against retroviruses (HIV-1 and HIV-2) and hepadnaviruses (HBV), whereas (*S*)-HPMPO-DAPy shows particular activity against adeno- and poxviruses [49].

The activity (potency) of (*S*)-HPMPO-DAPy against poxviruses (vaccinia, cowpox and orf) was similar to that of cidofovir, whereas the potency of 5-substituted PMEO-DAPy derivatives, such as 5-methyl-PMEO-DAPy, against HIV compared favorably with that of PMEA (EC_{50}: 0.09 μg/ml for 5-methyl-PMEO-DAPy against HIV-1, as compared to 2.9 μg/ml for PMEA) [49].

(*S*)-HPMPO-DAPy showed anti-adenovirus activity comparable to that of (*S*)-HPMPA and cidofovir [50], and the most potent among the PMEO-DAPy and (*R*)-PMPO-DAPy series of compounds showed activity against both wild-type and lamivudine-resistant HBV that was comparable to that of adefovir and tenofovir [51].

Further studies are required to assess the true potential of the ''DAPy'' phosphonates in the treatment of those virus infections where cidofovir, adefovir and tenofovir have left their marks. Also subject of further study are their pharmacokinetics, resistance profile and intracellular metabolism. It would be intriguing to decipher whether the ''DAPy'' phosphonates would be recognized (and metabolized) by enzymes involved in either purine or pyrimidine nucleoside/nucleotide metabolism.

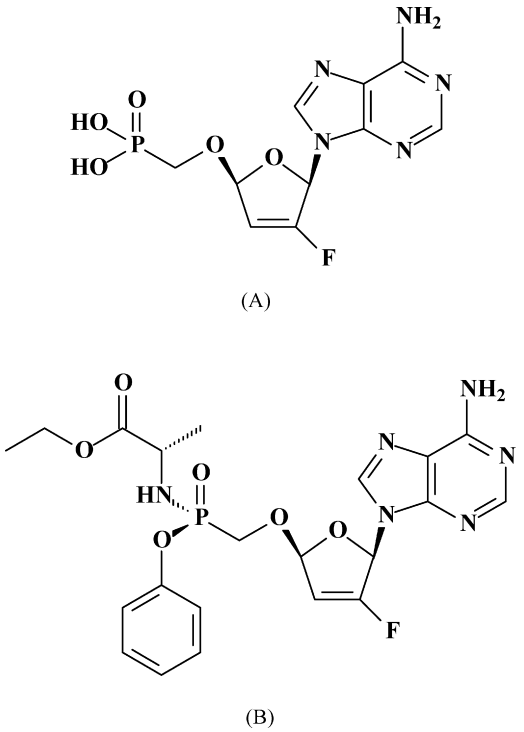


Fig. 13 – (A) GS9148 [53] and (B) GS9131: monophenol ethylalaninyl amidate prodrug of GS9148 [53].

6. New cyclic nucleoside phosphonates

Of a series of eight new phosphonate nucleosides with an L-threose or L-2-deoxythreose sugar moiety, two new compounds were identified (PMDTA and PMDTT) (Fig. 12) which showed potent activity against HIV [EC_{50}: 2.53 μM (PMDTA) and 6.59 μM (PMDTT)], while no cytotoxicity was observed at the highest concentration tested [CC: >316 μM (PMDTA) and >343 μM (PMDTT)] [52]. The kinetics of incorporation of PMDTA into DNA (using the diphosphate of PMDTA as substrate and HIV-1 reverse transcriptase as catalyst) was similar to the kinetics observed for dATP, while the diphosphate of PMDTA was a very poor substrate for cellular DNA polymerase α [52]. The incorporated PMDTA was found to fit very well within the active site pocket of HIV-1 reverse transcriptase.

GS9148 or phosphonomethoxy-2′-fluoro-2′,3′-dideoxy-2′,3′-didehydroadenosine represents another cyclic nucleoside phosphonate which was recently recognized as a potent anti-HIV agent [53] (Fig. 13A). This compound can be considered as the 2′-fluoro derivative of the phosphonate derivative of d4A, which has been previously described, and found to exhibit potent antiretroviral activity comparable to that of d4T [54].

From GS9148 (Fig. 13A) an ethylalaninyl amidate prodrug (GS9131) (Fig. 13B) has been derived [53]. This phosphoramidate prodrug of 2′-fluoro-d4A originated from the same concept that led to the design of GS7340, the phosphoramidate prodrug of tenofovir, which was found to be preferentially distributed to and accumulated in lymphatic tissue [55].

7. Future perspectives

Both acyclic and cyclic nucleoside phosphonates can now be contemplated as lead compounds for the design of new compounds for extending the current spectrum of antiviral activity of the acyclic nucleoside phosphonates, cidofovir, adefovir and tenofovir. Further modifications which could be envisaged may be introduced at the C-2′ position of either the cyclic or acyclic moiety of the (cyclic or acyclic) nucleoside phosphonates (Fig. 14). Whether the introduction of a fluorine, methyl or any other group in the C-2′ position of the (a)cyclic nucleoside phosphonate derivatives may ultimately lead to new antiviral agents, effective against (+)RNA viruses, such as the genus hepacivirus and in particular HCV (hepatitis C virus) remains to be established. Current knowledge dictates that combining the structural determinants for anti-HIV and anti-HBV activity with those governing anti-HCV activity, may indeed lead to new strategies for controlling HCV infections.

The phosphonate bridge has proven to be utmost successful in the fight against herpesvirus infections (cidofovir), hepatitis B (adefovir) and AIDS (tenofovir). Cidofovir yields great potential for the treatment of papilloma- and poxvirus infections, and tenofovir will be further pursued for the treatment of HBV infections. The phosphonate bridge (Fig. 15), thus extends to many viruses, encompassing HIV, HBV, HPV, adeno, herpes, pox, etc., and hopefully, HCV will not turn out to be one bridge too far.

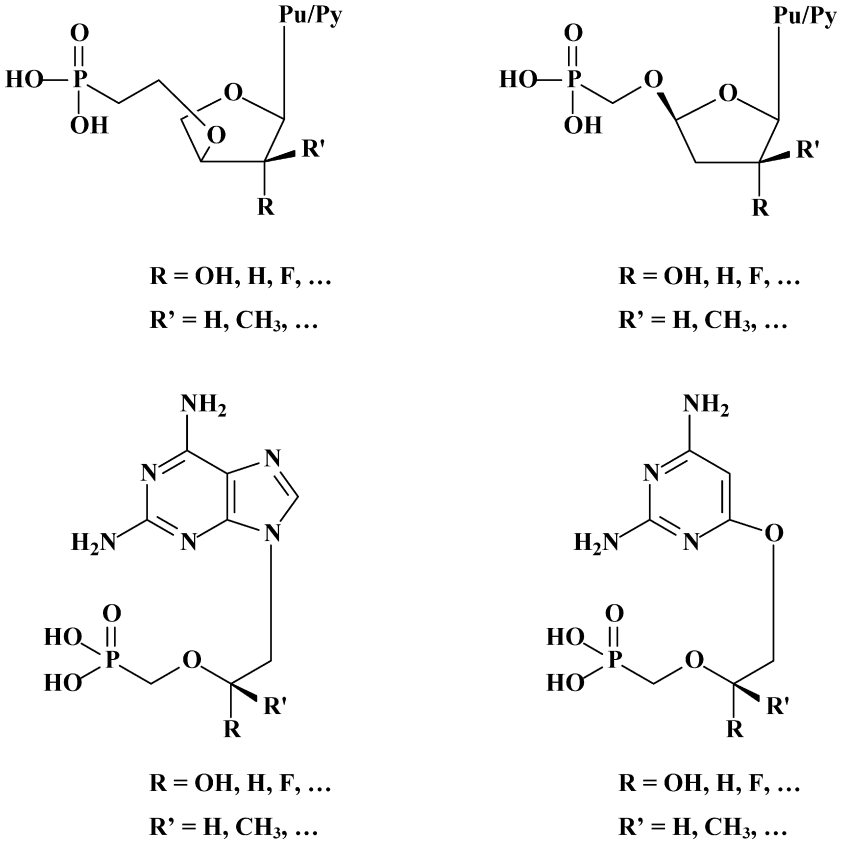


Fig. 14 – Hypothetical new (cyclic and acyclic) nucleoside phosphonates.

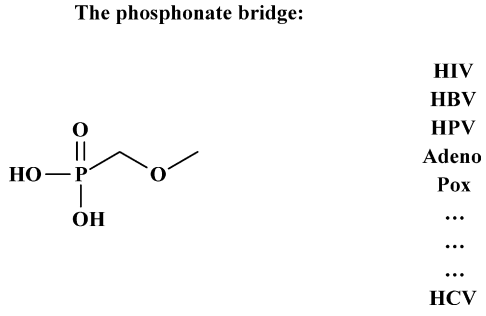


Fig. 15 – The phosphonate bridge.

8. Conclusion

There are at present five commercial preparations of acyclic nucleoside phosphonates available for the treatment of virus infections: Vistide® (cidofovir) for the treatment of HCMV retinitis in AIDS patients, and, off label, for the treatment of papilloma-, adeno-, herpes-, and poxvirus infections, in particular in immunocompromised patients; Hepsera® (adefovir dipivoxil) for the treatment of chronic HBV infections; Viread® (tenofovir disoproxil fumarate), Truvada® (tenofovir disoproxil fumarate plus emtricitabine) and Atripla® (tenofovir disoproxil fumarate plus emtricitabine plus efavirenz) for the treatment of HIV infections (AIDS).

Additional indications which are under current consideration include the use of the tenofovir disoproxil fumarate (TDF)-based drugs Viread and Truvada in the treatment of chronic HBV infections, and, even more importantly, the prophylactic use of Viread or Truvada in preventing HIV and HBV infections irrespective of the route of viral transmission (parenteral, sexual or perinatal). The availability of an oral medicine, to be taken as a single tablet once daily, would make the large-scale prophylactic usage feasible, if not attractive.

New acyclic (HPMPO-DAPy, PMEO-DAPy, PMPO-DAPy) and cyclic (PMDTA, PMDTT, GS9148) nucleoside phosphonates have been described which may be further pursued for any of the indications for which the presently available acyclic nucleoside phosphonates are applicable (HIV, HBV, papilloma-, adeno-, herpes- and poxviruses). Whether the ''phosphonate'' strategy may also extend to other viruses, such as hepatitis C virus, remains to be further explored.

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