Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
ABSTRACT

More than 40 compounds have been formally licensed for clinical use as antiviral drugs, and half of these are used for the treatment of HIV infections. The others have been approved for the therapy of herpesvirus (HSV, VZV, CMV), hepadnavirus (HBV), hepacivirus (HCV) and myxovirus (influenza, RSV) infections. New compounds are in clinical development or under preclinical evaluation, and, again, half of these are targeting HIV infections. Yet, quite a number of important viral pathogens (i.e. HPV, HCV, hemorrhagic fever viruses) remain in need of effective and/or improved antiviral therapies.

I. INTRODUCTION

There are at present a forty some antiviral drugs that have been formally licensed for clinical in the treatment of viral infections. These are mainly used in the treatment of infections caused by human immunodeficiency virus (HIV), hepatitis B virus (HBV), herpesviruses [herpes simplex virus (HSV), varicella-zoster virus (VZV),...}
cytomegalovirus (CMV)], orthomyxoviruses (influenza), paramyxoviruses [respiratory syncytial virus (RSV)], and hepaciviruses [hepatitis C virus (HCV)]. As these are the viruses that are most in demand of antiviral therapy, they have prompted the search for new antiviral strategies and drugs directed towards either the same molecular targets as the approved antiviral drugs or to other targets.

Most of the newly described antiviral compounds (that are currently in development) are targeted at HIV, HBV or HCV. Some are targeted at HSV, VZV or CMV, but, there are, in addition, many other important viral pathogens for which medical intervention, either prophylactic or therapeutic, is highly needed, and, these are, among the DNA viruses, the papillomaviruses [human papilloma virus (HPV)], adenoviruses, poxviruses (variola, vaccinia, monkeypox, ...) and the herpesviruses Epstein–Barr (EBV) and human herpesvirus type 6 (HHV-6), and, among the RNA viruses, enteroviruses (i.e. Coxackie B and Echo), coronaviruses [i.e. severe acute respiratory syndrome (SARS)-associated coronavirus], flaviviruses (i.e. Dengue, Yellow fever) and other RNA viruses associated with hemorrhagic fever [arenaviruses (i.e. Lassa fever), bunyaviruses (i.e. Rift Valley fever, Crimean-Congo fever) and filoviruses (i.e. Ebola and Marburg)].

Here I will describe, for each viral family, (i) which are the antiviral drugs that have been formally approved, (ii) which are the compounds that are under clinical development and thus may be considered as antiviral drug candidates, and (iii) which compounds are in the preclinical stage of development and still have a long route ahead before they could qualify as antiviral drugs (Table 1, Figure 1). The virus families to be addressed are the following: parvo-, polyoma-, papilloma-, adeno-, herpes-, pox-, picorna-, flav-, corona-, orthomyxo-, paramyxo-, arena-, bunya-, rhabdo-, filo-, reo-, and retroviruses.

II. PARVOVIRUSES

No significant attempts have been made to develop compounds with potential activity against B19, the only parvovirus that is pathogenic for humans and responsible for erythema infectiosum, the so-called fifth disease, in children.

III. POLYOMAVIRUSES

No antiviral drugs have been formally approved for the treatment of polyomavirus (JC and BK)-associated diseases such as progressive
multifocal leukoencephalopathy (PML) and hemorrhagic cystitis in patients with AIDS. There are, however, anecdotal case reports pointing to the efficacy of cidofovir [(S)-1-(3-hydroxy-2-phosphonylmethoxypropyl)cytosine, HPMPC], which has been licensed under the trademark name Vistide® for the intravenous treatment of CMV retinitis in AIDS patients] in the treatment of polyoma (JC and BK) virus infections, particularly PML, in AIDS patients.39

The in vitro activity of various acyclic nucleoside phosphonates, among which HPMPC (cidofovir), against murine and primate polyomaviruses has been well established.1 Esterification of cidofovir (CDV) with hexadecyloxypropyl (HDP) or octadecyloxyethyl (ODE) groups, as in HDP-CDV or ODE-CDV, respectively, resulted in up to a 3-log decrease of the 50% effective concentration (EC50) and up to 2-log increase of the selectivity index.130

IV. PAPILLOMAVIRUSES

As for polyomaviruses, no antivirals have been licensed for the treatment of human papillomavirus (HPV)-associated diseases, including warts (verruca vulgaris), condyloma acuminatum, papillomatosis (i.e. recurrent respiratory papillomatosis), and cervical, vulvar, penile and (peri)anal dysplasia (evolving to carcinoma). Various strategies, including surgery and other destructive therapies, antiproliferative agents, and immunotherapies have been used for the treatment of HPV-associated lesions.141 Cidofovir has been used “off label”, with success, in the topical and, occasionally, systemic treatment of HPV-associated papillomatous lesions.39 In many instances, a virtually complete and durable resolution of the lesions was achieved following topical application of cidofovir as a 1% gel or cream.

In addition to cidofovir, other acyclic nucleoside phosphonates, such as cPrPMEDAP [N6-cyclopropyl-9-(2-phosphonylmethoxyethyl)-2,6-diaminopurine], are being explored for their potential in the treatment of HPV-associated papillomas and dysplasias.39,51 These compounds have been shown to specifically induce apoptosis in HPV-infected cells, which, in turn, may be related to their ability to restore the function of the tumor suppressor proteins p53 and pRb (which are neutralized by the oncoproteins E6 and E7, respectively, in HPV-infected cells).

Recently, biphenylsulphonacetic acid derivatives have been described as inhibitors of HPV E1 helicase-associated ATP hydrolysis.60,155 Although these novel ATPase inhibitors can hardly be considered to be
good drug candidates, they may serve as leads for further optimization as potential antiviral agents active against multiple HPV types.\textsuperscript{155}

As for so many other virus infections (see \textit{supra}), RNA interference (RNAi), based on small interfering RNAs, has been advocated to block HPV infections (HPV16 E6 oncogene expression).\textsuperscript{118,148} This siRNA approach could be particularly useful for silencing HPV oncogenes, as in cervical intraepithelial neoplasia.

\textbf{V. ADENOVIRUSES}

For the treatment of adenovirus infections, which could be quite severe in immunocompromised patients (i.e. allogeneic hematopoietic stem-cell transplant recipients), no antiviral drugs have been officially approved. Anecdotal reports have pointed to the efficacy of cidofovir against adenovirus infections in such patients.\textsuperscript{39} Among the novel compounds that could be further explored for the treatment of adenovirus infections are (\textit{S})-2,4-diamino-6-[3-hydroxy-2-phosphonomethoxy]propoxy]pyrimidine [HPMPO-DAPy],\textsuperscript{51} which akin to some “older” compounds like (\textit{S})-9-(3-hydroxy-2-phosphonomethoxypropyl)adenine (HPMPA), the N7-substituted acyclic nucleoside 2-amino-7-(1,3-dihydroxy-2-propoxymethyl)purine S-2242, the 2',3'-dideoxynucleosides zalcitabine (ddC) and alovudine (FddT, FLT) have been found to inhibit adenovirus replication \textit{in vitro}.\textsuperscript{113}

In fact, ddC was also found effective \textit{in vivo}, in a mouse model for adenovirus pneumonia.\textsuperscript{111} Also, ether lipid-ester [hexadecyloxypropyl (HDP) and octadecyloxyethyl (ODE)] prodrugs of HPMPC and HPM-PAI have been designed that inhibit adenovirus replication \textit{in vitro} at significantly lower concentrations than the parent compounds.\textsuperscript{73}

\textbf{VI. \textit{\alpha}-HERPESVIRUSES (HSV-1, HSV-2, VZV)}

For the treatment of HSV-1, HSV-2 and VZV, a number of compounds have been approved: acyclovir and its oral prodrug valaciclovir; penciclovir and its oral prodrug, famciclovir; idoxuridine, trifluridine and brivudin. Penciclovir, idoxuridine and trifluridine are used topically, primarily in the treatment of herpes labialis (penciclovir) and herpetic keratitis (idoxuridine, trifluridine). Acyclovir can be used orally, intravenously or topically, whereas valaciclovir and famciclovir are administered orally, in the treatment of both HSV and VZV infections. Brivudin (available in some European countries) is used orally for the
treatment of herpes zoster, but is also effective against HSV-1 infections.

While acyclovir (and its oral prodrug valaciclovir) have remained the gold standard for the treatment of HSV and VZV infections, few attempts have been made to bring other anti-HSV (or anti-VZV) agents into the clinic, with the exception of the H2G prodrug, which, since quite a number of years, is still in clinical development for the treatment of herpes zoster. From acyclovir (ACV) and ganciclovir (GCV) tricyclic derivatives, i.e. tricyclic acyclovir (TACV), and 6-substituted derivatives thereof which have similar (or only slightly decreased) antiviral potency but increased lipophilicity as compared to the parent compounds (ACV and GCV), and, in addition, show interesting fluorescence properties.

Worth considering for clinical development as anti-HSV (and anti-VZV) agents are a number of carbocyclic guanosine analogues, such as A-5021, cyclohexenylguanine, and the methylene cyclopropane syn-guanol. All these compounds owe their selective antiviral activity to a specific phosphorylation by the HSV- or VZV-encoded thymidine kinase (TK); upon phosphorylation to their triphosphate form, they act as chain terminators in the DNA polymerization reaction. In the (rare) circumstances that HSV or VZV becomes resistant to the acyclic (or carbocyclic) guanosine analogues due to TK deficiency (TK−), the pyrophosphate analogue foscarnet could be useful to treat TK− HSV or TK− VZV infections (in immunocompromised patients).

Recently, a second generation of methylene cyclopropane analogues, the 2,2-bishydroxymethyl derivatives, has been synthesized. These compounds may have potential, not only for the treatment of HSV-1, HSV-2 and VZV, but also β-herpes (CMV, HHV-6, HHV-7) and γ-herpes (EBV, HHV-8) infections. In particular, ZSM-I-62 (Cyclopropavir) has been reported to be very effective in reducing mortality of mice infected with murine CMV. Of a recently synthesized series of 9-[(3-fluoro-2-(hydroxymethyl)cyclopropylidene)methyl]adenines and guanines, the (Z)-[(trans)-(3-fluoro-2-hydroxymethyl)cyclopropylidene]methyl]adenine was quoted as being effective against EBV at an EC50 < 0.03 µM.

New anti-HSV agents targeting the viral helicase–primase complex, the thiazolylphenyl derivatives BILS 179 BS and BAY 57-1293, were recently reported to have in vivo efficacy in animal models of HSV-1 and HSV-2 infections. These compounds seem to function by diminishing the affinity of the helicase–primase complex for the HSV DNA. The heterotrimeric helicase–primase complex is composed of the UL5, UL8 and UL52 gene products with DNA helicase DNA-dependent ATPase and DNA primase activity. Resistance to
aminothiazolylphenyl-based inhibitors has been shown to arise from single amino acid changes in the UL5 protein.\textsuperscript{103}

The antiviral potency of BAY 57-1293 was reported to be superior to all compounds that are currently used to treat HSV infections.\textsuperscript{13} In recent studies, BAY 57-1293 was shown to be more efficacious than famciclovir in the therapy of HSV-1 infections in BALB/C mice.\textsuperscript{16} Also, BILS 45BS, which is structurally related to BILS 179 BS, exhibited excellent efficacy in the oral treatment of acyclovir-resistant (ACV\textsuperscript{r}) HSV-1 infections in nude mice,\textsuperscript{57} highlighting the potential of this class of antiviral agents for the treatment of ACV\textsuperscript{r} HSV disease in humans.

RNA interference (RNAi), as generated by small interfering RNAs (siRNAs), has been recently pursued as a powerful tool to silencing disease,\textsuperscript{138} including viral infections. Palliser et al.\textsuperscript{123} have shown that vaginal instillation of siRNAs targeting the HSV-2 UL27 and UL29 genes (which encode an envelope glycoprotein and a DNA binding protein, respectively) protected mice from a lethal HSV-2 infection; the siRNAs were mixed with lipid so as to ensure their uptake by the cells (vagina and ectocervix). From this study it was concluded that siRNAs may be attractive candidates for application as microbicides to prevent viral infection.\textsuperscript{123}

A new class of anti-VZV compounds are the bicyclic furo (2,3-d)pyrimidine nucleoside analogues (BCNAs), represented by Cf 1742 and Cf 1743.\textsuperscript{110} These compounds are exquisitely active against VZV.\textsuperscript{40} They inhibit the replication of VZV, but not that of other viruses (including HSV), at subnanomolar concentrations, with a selectivity index in excess of 100,000.\textsuperscript{2} Given the extremely high potency and selectivity of the BCNAs they warrant to be further developed towards clinical use, i.e. against herpes zoster.

\section*{VII. $\beta$-HERPESVIRUSES (CMV, HHV-6, HHV-7)}

Five compounds have been licensed to treat CMV infections: ganciclovir, its oral prodrug valganciclovir, foscarnet, cidofovir and fomivirsen. [Foscarnet has also proven efficacious in the treatment of other DNA virus (i.e., hepatitis B) infections.\textsuperscript{72} With the exception of fomivirsen (an antisense oligonucleotide) which targets the CMV immediate-early mRNA, all other licensed anti-CMV drugs target the viral DNA polymerase. Ganciclovir must first be phosphorylated by the CMV-encoded protein kinase (the UL97 gene product) which is also the principal site for mutations engendering resistance towards this compound. Toxic
side effects (i.e. bone–marrow suppression for ganciclovir, nephrotoxicity for foscarnet and cidofovir) have prompted the search for new inhibitors of CMV.41

Several benzimidazole ribonucleosides, among which maribavir (previously also known as 1263W94), have been accredited with specific activity against human CMV. Maribavir seems to target the UL97 protein kinase,15 and, as the UL97 gene product has been shown to account for the release of CMV nucleocapsids from the nucleus,90 maribavir may be assumed to target a stage in the viral life cycle that follows viral DNA maturation and packaging. Preclinical pharmacokinetic and toxicological studies have shown that maribavir has a favorable safety profile and excellent oral bioavailability.89

Phase I/II dose-escalation trials in HIV-infected men with asymptomatic CMV shedding further indicated that maribavir is rapidly absorbed following oral dosing and reduces CMV titers in semen.93 Maribavir is currently in a prophylaxis study in allogenic stem cell transplant recipients with results expected in 2006 [to be divulged by ViroPharma Inc., according to Biron14]. Biron14 also mentioned two other compounds, i.e. BAY 38-4766 and GW275175X, which entered clinical development but were then not further developed despite a favorable safety profile (BAY 38-4766) or shelved in favor of the advancement of maribavir (GW275175X).

While maribavir is primarily active against CMV, 2-chloro-3-pyridin-3-yl-5,6,7,8-tetrahydroindolizine-1-carboxamide (CMV423) has potent and selective in vitro activity against all three human β-herpesviruses, CMV, HHV-6 and HHV-7.35,36 As compared to ganciclovir and foscarnet, CMV423 has higher antiviral potency and lower cytotoxicity. It is targeted at an early stage of the viral replication cycle (following viral entry but preceding viral DNA replication), which is regulated by a cellular process that may involve protein tyrosine kinase activity.

Some cellular kinase inhibitors have been found to enhance the antiviral activity of maribavir.26 It may be useful, therefore, to further explore the possibility of therapeutically useful combinations of maribavir and cellular kinase inhibitors such as CMV423. Combination of maribavir with ganciclovir should not be recommended, since maribavir antagonizes the antiviral action of ganciclovir.25

Alkoxyalkyl esters of cidofovir (i.e. HDP-CDV) have been developed that retain the efficacy of the parent compound,10 without the associated renal toxicity28 and with significantly improved oral bioavailabilities. HDP-CDV (CMX001) is under current development as an oral drug for the treatment of poxvirus infections as well as CMV and other herpesvirus infections.
There is, at present, no standardized antiviral treatment for HHV-6 infections and also their potential clinical indications remain ill-defined. From a comparative study, A-5021, foscarnet, S2242, and cidofovir emerged as the most potent compounds with the highest antiviral selectivity against HHV-6. The latter three also proved to be the most potent against HHV-7. In addition to cidofovir, HPMPA and its 3-deaza analogue 3-deaza-HPMPA have also been identified as potent and selective inhibitors of HHV-6 replication.

However, the most promising anti-HHV-6 activity was demonstrated by CMV423, a compound that has been shown previously to be highly effective in vitro against CMV. The compound exhibited a potency (EC\(_{50}\): 0.02–0.05 µM) and selectivity (SI > 2000) against HHV-6(A), which by far exceeded that of the standard anti-herpesvirus agents acyclovir, ganciclovir, foscarnet and cidofovir. The in vitro antiviral action profile of CMV423 is such that it deserves to further explored for its in vivo potential in the treatment of CMV and HHV-6(A) infections.

**VIII. ɣ-HERPESVIRUSES (EBV, HHV-8)**

Although a number of the aforementioned approved anti-herpetic drugs, such as acyclovir, ganciclovir, brivudin and cidofovir, have proven to be effective against the in vitro replication of EBV and HHV-8, none of these (or any other) antiviral drugs have been formally approved for the treatment of diseases associated with EBV (i.e. mononucleosis infectiosa, B-cell lymphoma, lymphoproliferative syndrome, Burkitt’s lymphoma, nasopharyngeal carcinoma) or HHV-8 (Kaposi’s sarcoma, primary effusion lymphoma, multicentric Castleman’s disease). It would seem appealing to further examine established anti-herpetic drugs, such as cidofovir, and other acyclic nucleoside phosphonates such as HPMPA, or prodrugs thereof, for their potential in the therapy of EBV- and HHV-8-associated malignancies.

Also, new nucleoside analogues, such as the conformationally locked nucleoside analogue north-methanocarbathymidine [(N)-MCT], which have been previously shown to block the replication of HSV-1 and HSV-2, should be further explored for their potential in the prevention and treatment of HHV-8-associated malignancies: in casu, (N)-MCT, which is specifically triphosphorylated in HHV-8-infected cells undergoing lytic replication efficiently blocks HHV-8 DNA replication in these cells. In fact, the antiviral activity spectrum of (N)-MCT not only includes ɣ-herpesviruses (EBV, HHV-8) and α-herpesviruses (HSV-1, HSV-2, VZV) but also poxviruses. (N)-MCT would be activated
by the viral thymidine kinase (TK) homologs and inhibit the viral DNA polymerase. The compound has been demonstrated to be effective in vivo in reducing the mortality of mice infected with HSV-1 or orthopoxviruses.125

IX. POXVIRUSES (VARIOLA, VACCINIA, MONKEYPOX, MOLLUSCUM CONTAGIOSUM, ORF . . .)

Thiosemicarbazenes, i.e. isatin-β-thiosemicarbazone and N-methyl-isatin-β-thiosemicarbazone (marboran or methisazone) were investigated in the 1960s for their efficacy against orthopoxviruses. They have had a lengthy history as prophylactic therapeutics with potential efficacy against Mycobacterium tuberculosis. However, it has become recently clear that this class of compounds has little, if any, potential for orthopoxvirus infections (i.e. cowpox virus, a surrogate virus for variola virus).129

Several nucleoside analogues (i.e. S2242, 8-methyladenosine, idoxuridine) and nucleotide analogues (i.e. cidofovir, HPMPO-DAPy,) have proven to be effective in various animal models of poxvirus infections.48 In particular, cidofovir has shown high efficacy, even after administration of a single systemic (intraperitoneal) or intranasal (aerosolized) dose, in protecting mice from a lethal respiratory infection with either vaccinia or cowpox. Cidofovir has demonstrated high effectiveness in the treatment of disseminated progressive vaccinia in athymic-nude mice.115

In humans, cidofovir has been used successfully, by both the topical and intravenous route, in the treatment of orf and recalcitrant molluscum contagiosum in immunocompromised patients.38 Cidofovir (HPMPC) and its congeners (HPMPDAP and HPMPO-DAPy) are highly effective against orf in human and ovine cell monolayers and organotypic ovine raft cultures.31 Given the in vitro activity of cidofovir against variola (smallpox) and other poxviruses, and the in vivo efficacy of cidofovir against various poxvirus infections in animal models and humans, it can be reasonably assumed that cidofovir should be effective in the therapy and/or prophylaxis of smallpox in case of an inadvertent outbreak or biological attack with the variola virus.

Being a phosphonate analogue, cidofovir only has limited oral bioavailability. In case of an outbreak of smallpox, it would be useful to have an orally active drug at hand.122 To this end, hexadecyloxypropyl-cidofovir (HDP-CDV) and octadecyloxyethyl-cidofovir (ODE-CDV) were
designed as potential oral prodrugs of cidofovir. These alkyloxyalkyl esters of cidofovir were found to significantly enhance inhibition of the replication of orthopoxviruses (i.e. vaccinia, cowpox) \textit{in vitro}. \textsuperscript{83} HDP-CDV and ODE-CDV given orally were as effective as cidofovir given parenterally for the treatment of vaccinia and cowpox infections. \textsuperscript{128}

HDP-CDV has proven effective in the treatment of a lethal vaccinia virus respiratory infection in mice. \textsuperscript{140} Furthermore, HDP-CDV and ODE-CDV, when given orally, proved highly efficacious in a lethal (aerosol) mousepox (ectromelia) virus model,\textsuperscript{19} further attesting as to the potential usefulness of the alkyloxyalkyl esters of cidofovir in the oral therapy and prophylaxis of poxvirus infections. This potential usefulness has been recently extended to the alkoxyalkyl esters of (S)-9-(3-hydroxy-2-phosphonylmethoxypropyl)adenine (HPMPA) for the treatment of orthopoxvirus (i.e. vaccinia, cowpox) as well as cytomegalovirus infections.\textsuperscript{95,11}

In fact, as indicated by the most recent findings with cidofovir in mice infected with ectromelia (mousepox) virus encoding interleukin-4,\textsuperscript{132} and monkeys infected with monkeypox,\textsuperscript{145} cidofovir (CDV) (and HDP-CDV and/or ODE-CDV) still provide the best current hope for effective control of virulent poxvirus infections.

Mutations in the E9L polymerase gene, i.e. A314T and A684V, of vaccinia virus have been associated with cidofovir resistance.\textsuperscript{3} Cidofovir resistance was associated with diminished virulence and reduced fitness \textit{in vivo}, in mice.\textsuperscript{3} Cidofovir (CDV) still protected mice against CDV-resistant vaccinia virus.\textsuperscript{3,88}

In addition to the nucleotide analogue cidofovir, which primarily acts as a viral DNA chain terminator (for vaccinia virus DNA polymerase after it has been incorporated at the penultimate position),\textsuperscript{105} antiviral strategies for poxvirus infections may also be based on inhibitors of cellular processes, i.e. signal transduction pathways. In this respect, the 4-anilinoquinazoline Cl-1033, an ErbB tyrosine kinase inhibitor, was found to block variola virus replication \textit{in vitro} and vaccinia virus infection \textit{in vivo}.\textsuperscript{159}

Likewise, Gleevec\textsuperscript{®} (STI-571, Imatinib), an Abl-family kinase inhibitor used to treat chronic myelogenous leukemia in humans was shown to suppress poxviral dissemination \textit{in vivo} by several orders of magnitude and to promote survival in infected mice,\textsuperscript{131} suggesting possible use for this drug in treating smallpox or complications associated with vaccination against smallpox. Because the drug targets host rather than viral molecules, it is less likely to engender resistance compared to more specific antiviral agents. Collectively,\textsuperscript{159,131} inhibitors of
host-signaling pathways exploited by poxviral pathogens may represent potential antiviral therapies.

Recently, a new anti-poxvirus compound (ST-246) has been described, which is orally bioavailable, acts according to a novel mechanism of action, targeting a specific viral product (i.e. vaccinia virus F13L) required for extracellular virus particle formation and protecting mice from a lethal orthopoxvirus challenge. These properties make ST-246 an attractive candidate for development as a smallpox antiviral drug that could be stockpiled for use in the treatment and prevention of smallpox virus infection in the event of a bioterrorist threat.

As already mentioned above, a wealth of nucleoside analogues, i.e. 5-substituted 2′-deoxyuridines (5-X-dUrds, related to idoxuridine) and neplanocin analogues, have been described as potent inhibitors of vaccinia virus [as the paradigm of poxviruses]. Several new congeners have been recently added to this list: i.e. 5-(dimethoxymethyl)-2′-deoxyuridine, pyrazolone-pyrimidine-2′-deoxynucleoside chimera, and a cyclopentenyl 1,2,3-triazole-4-carboxamide. As has been demonstrated for many other viruses, small-interfering (si)RNAs have also proved effective against vaccinia virus, i.e. E3L-specific siRNAs targeting the double-stranded (ds)RNA binding protein E3L.

X. HEPADNAVIRUSES (HBV)

An estimated 400 million people worldwide are chronically infected with the hepadnavirus HBV; approximately 1 million die each year from complications of infection, including cirrhosis, hepatocellular carcinoma, and end-stage liver disease. Formally approved for the treatment of chronic hepatitis B are lamivudine, adefovir dipivoxil, (pegylated) interferon-α2 and entecavir. Whereas lamivudine, adefovir and entecavir [and other nucleoside analogues which are still in (pre)clinical development] act as genuine antiviral agents at the HBV-associated reverse transcriptase, interferon, in the chronic hepatitis B setting, primarily acts as an immunomodulator.

Pegylated interferon-α2b is effective in the treatment of HBeAg-positive chronic hepatitis B, but no additional benefit is achieved if it is combined with lamivudine. Nor does the addition of ribavirin seem to increase the efficacy of interferon in the treatment of HBeAg-positive chronic hepatitis B. Combination of pegylated interferon α-2b with adefovir dipivoxil, however, led to a marked decrease in serum HBV DNA and intrahepatic covalently closed circular DNA (cccDNA); which
was significantly correlated with HBsAg reduction in patients with chronic hepatitis B.\textsuperscript{157}

Whereas interferon therapy, also because of its unavoidable side effects (influenza-like symptoms) is not recommended for a duration longer than 1 year, the nucleos(t)ide analogues can, in principle, be administered for quite a number of years. For lamivudine (3TC), however, this prolonged treatment if compounded by the emergence of both virological and clinical resistance at an accumulating rate of approximately 20 percent of the patients per year (70\% after 4 years of treatment). This resistance is primarily due to the emergence of the rt M204 I/V mutation in the YMDD motif of the HBV DNA polymerase [although, as has recently been demonstrated, lamivudine-resistant mutations can also emerge outside the YMDD motif].\textsuperscript{161}

Resistance to adefovir dipivoxil may also emerge, but less frequently: not more than 6 percent after 3 years,\textsuperscript{71} although it may rise to 18 percent after 4 years\textsuperscript{106} and 29\% of patients after 5 years of therapy [as cited by Osborn and Lok].\textsuperscript{120} Adefovir dipivoxil is the oral prodrug of adefovir [PMEA, 9-(2-phosphonylmethoxyethyl)adenine], which, after intracellular conversion to the diphosphate form, acts as a competitive inhibitor or alternative substrate for the HBV reverse transcriptase, and, when incorporated into the DNA, acts as a chain terminator, thereby preventing DNA chain elongation.\textsuperscript{42}

In patients with chronic HBV infection who were either positive\textsuperscript{107} or negative\textsuperscript{70} for hepatitis B e-antigen, 48 weeks of treatment with a dose of adefovir dipivoxil as low as 10 mg per day resulted in significant improvement of all parameters of the disease (histological liver abnormalities, serum HBV DNA titers and serum alanine aminotransferase levels). In patients with HBeAg-negative chronic hepatitis B, the benefits achieved from 48 weeks of adefovir dipivoxil were lost when treatment was discontinued, but maintained if treatment was continued through week 144.\textsuperscript{71} Adefovir dipivoxil (10 mg daily) treatment over 52 weeks proved safe and effective in Chinese subjects with HBeAg-positive chronic hepatitis B and during this period did not lead to emergence of drug resistance.\textsuperscript{165}

Resistance to adefovir dipivoxil is associated with the rt N236T and rt A181V/T mutations,\textsuperscript{121} as demonstrated in samples from patients with chronic HBV infection. Emergence of the rt A181V/T and rt N236T mutations is more common in lamivudine-resistant patients than in treatment-na\textsuperscript{ive} patients.\textsuperscript{98} Adefovir resistance can be associated with viral rebound, hepatitis flares and hepatic decompensation.\textsuperscript{64} It has been suggested to combine lamivudine with adefovir dipivoxil, even in patients with lamivudine-resistant HBV, so as to
prevent emergence of adefovir resistance. In fact, adefovir dipivoxil should be added, i.e. in HBeAg-negative patients, to lamivudine as soon as genotypic resistance to lamivudine has developed.

Entecavir, one of the most recent antiviral drugs launched for clinical use, has in vitro and in vivo potency that seems to be greater than that of lamivudine: in patients with chronic hepatitis B infection it has proven efficacious at a dose as low as 0.5 mg per day. The active (triphosphate) metabolite of entecavir would accumulate intracellularly at concentrations that are inhibitory to 3TC-resistant HBV DNA polymerase. It is not clear, however, how this translates to clinical efficacy of entecavir against lamivudine-resistant HBV infections. Early studies of entecavir indicate a low resistance potential, but resistance development over time must await the results of ongoing clinical trials.

Comprehensive studies with entecavir carried out in patients with either HBeAg-positive chronic hepatitis B or HBeAg-negative chronic hepatitis B pointed out that the rates of histologic improvement, virologic response, and normalization of alanine aminotransferase levels were significantly higher at 48 weeks of treatment with entecavir than with lamivudine. No case of resistance was detected after two years of entecavir therapy in patients who had not been previously treated with lamivudine. However, 10% of those patients that had failed on lamivudine therapy developed entecavir resistance after two years of therapy.

A number of L-nucleosides, i.e. β-L-thymidine (L-dT, Telbivudine), the 3′-valine ester of β-L-2′-deoxycytidine (Val-L-dC, Valtorcitabine) and 1-(2-fluoro-5-methyl-β-L-arabinosyl)uracil (L-FMAU, Clevudine) are in clinical development for the treatment of chronic hepatitis B. As far as the role of deoxythymidylate (dTMP) kinase in the metabolism of clevudine is concerned, clevudine showed potent antiviral activity, which was sustained for 6 months after a 12-week treatment period in HBeAg-positive chronic hepatitis B patients. Telbivudine did not show drug interaction with lamivudine or adefovir dipivoxil, which would allow combination of telbivudine with these drugs from a pharmacokinetics viewpoint.

Other compounds in preclinical development include 2′,3′-dideoxy-3′-fluoroganosine (FLG), racivir and L-Fd4C. These compounds are also active against HIV (see Part II). FLG proved equally effective against wild-type, lamivudine-resistant and/or adefovir-resistant HBV mutants. A new class of chemicals, represented by helioxanthin, has been recently described: these compounds would inhibit HBV repli-
cation by a mechanism of action that is different from any other anti-HBV agents described so far.\textsuperscript{23} Moreover, tenofovir disoproxil fumarate (TDF) and emtricitabine [(\(-\)FTC, the 5-fluoro-substituted counterpart of lamivudine)], which have both been licensed, individually and in combination, for the treatment of HIV infections (AIDS), may also be considered and further pursued, individually or in combination, for use in the treatment of chronic hepatitis B. TDF has been considered an important new therapeutic tool for the induction of complete remission in patients with lamivudine-resistant HBV infection;\textsuperscript{150} it may be a highly effective rescue drug for HBV-infected patients with diminished responsiveness to treatment with lamivudine and adefovir dipivoxil.\textsuperscript{151} At the dose used for the treatment of HIV infections, that is 300 mg/day, TDF has been found effective against wild-type and lamivudine-resistant HBV strains in HBV/HIV-coinfected patients.\textsuperscript{12}

Like TDF, emtricitabine [(\(-\)FTC] has activity against both HIV and HBV, and should, therefore, be considered for use in patients coinfected with HIV and HBV.\textsuperscript{135} An interesting recommendation has been proposed for the care of patients with chronic HBV and HIV co-infection.\textsuperscript{143} They should be put on the combination of TDF with (\(-\)FTC, which would cover both the HBV and HIV infection. Only if no antiretroviral therapy would be used in these patients, adefovir dipivoxil and/or pegylated interferon may be installed depending on whether they are HBeAg-negative or -positive, respectively.\textsuperscript{143}

As has been shown for many other viruses, the RNA interference (RNAi) approach based on short interfering RNAs (siRNAs) can also be applied to specifically inhibit HBV replication \textit{in vitro}, in cell culture,\textsuperscript{163,124} and \textit{in vivo}, in mice transfected with an HBV plasmid.\textsuperscript{109} In fact, several studies have demonstrated that siRNAs are capable of specifically inhibiting HBV replication \textit{in vivo}\textsuperscript{109,86,67} and thus may constitute a new therapeutic strategy for HBV infection.

\section*{XI. RETROVIRUSES (HIV)}

There are at present twenty some compounds available for the treatment of HIV infections.\textsuperscript{45} These compounds fall into 5 categories: (i) nucleoside reverse transcriptase inhibitors (NRTIs): zidovudine, didanosine, zalcitabine, stavudine, lamivudine, abacavir and emtricitabine; (ii) nucleotide reverse transcriptase inhibitors (NtRTIs): tenofovir disoproxil fumarate; (iii) non-nucleoside reverse transcriptase inhibitors (NNRTIs): nevirapine, delavirdine and efavirenz; (iv) protease
inhibitors (PIs): saquinavir, ritonavir, indinavir, nelfinavir, amprenavir, lopinavir (combined at a 4 to 1 ratio with ritonavir), atazanavir, fosamprenavir, tipranavir and darunavir; and (v) fusion inhibitors (FIs): enfuvirtide. Several of these compounds are also available as fixed dose combinations: zidovudine with lamivudine (Combivir®), lamivudine with abacavir (Kivexa®), and emtricitabine with tenofovir disoproxil fumarate (Truvada®). A triple-drug fixed dose combination, containing efavirenz, emtricitabine and tenofovir disoproxil fumarate (Atripla®) has recently been launched.

In addition to the 22 licensed anti-HIV compounds, various others are (or have been) in clinical [phase II (or III)] development: the HIV-1 attachment inhibitors BMS-378806 and BMS-488043, the CXCR4 antagonist AMD-3100 (as stem cell mobilizer for stem cell transplantation in patients with non-Hodgkin lymphoma or multiple myeloma), the CCR5 antagonists SCH-C, vicriviroc (SCH-D, SCH 417690), aplaviroc (873140) and maraviroc (UK-427,857), the NRTIs racicrivir, (-)-dOTC [AVX-754 (SPD-754), which has been accredited with activity against most other NRTI-resistant HIV-1 strains], reverset, elvucitabine, alovudine and amdoxovir, the NNR-TIs capravirine and etravirine, the protease inhibitor (PI) darunavir (TMC-114) (which, in the mean time, has been approved for clinical use), and the gag (p24) maturation inhibitor 3-O-(3′,3′-dimethylsuccinyl)-betulinic acid (PA-457). Also, a prodrug of the benzophenone GW 678248 has recently progressed to phase II clinical studies.

The protease inhibitor brecanavir (GW 640385) has progressed to phase II/III clinical trials. Although brecanavir can engender, on its own, in vitro drug resistance development, co-administration of brecanavir (300 mg) with ritonavir (100 mg) significantly increased the plasma brecanavir levels, achieving drug concentration predicted to inhibit protease inhibitor-resistant HIV mutants. Pharmacokinetic boosting with sub-therapeutic doses of ritonavir has become a standard procedure to enhance systemic drug exposures for a variety of the HIV protease inhibitors.

Yet other compounds are in preclinical development and/or may soon proceed to clinical phase I/II clinical studies: the CD4 (HIV receptor) down-modulator cyclotriazadisulfonamide (CADA); the HIV gp120 envelope-binding protein cyanovirin-N as a topical microbicide; KRH-2731, a CXCR4 antagonist, structurally related to KRH-1636; the CXCR4 antagonist AMD-070 (a derivative of the bicyclam AMD3100, which is currently being pursued in phase II/III clinical trials, in combination with granulocyte colony-stimulating factor (G-CSF), for the mobilization of autologous hematopoietic progen-


Table 1. The past, present and future of antiviral drugs (Part I: DNA viruses and retroviruses)

| Virus                  | Compound                                                                 |
|------------------------|--------------------------------------------------------------------------|
|                        | Approved for medical use | In clinical development | In preclinical evaluation                                      |
| Parvo (B19)            |                           |                          | –                                                              |
| Polyoma (JC, BK)       |                           |                           | –                                                              |
| Papillomas (HPV)       |                           |                           | cPr PMEDAP and other acyclic nucleoside phosphonates Biphenylsulphonacetic acid derivatives |
| Adeno                  | Cidofovir (“off label”)       |                           | HPMPO-DAPy HDP-HPMPA, ODE-HPMPA                              |
| α-Herpes (HSV-1, HSV-2, VZV) | Acyclovir          | H2G prodrug               | Tricyclic acyclovir derivatives                               |
|                        | Valaciclovir             |                           | A-5021 Synguanol                                            |
|                        | Penciclovir (topical)    |                           | Cyclopropavir (ZSM-I-62)                                    |
|                        | Famciclovir              |                           | BILS 45 BS                                                  |
|                        | Brivudin                  |                           | BAY 57-1293                                                 |
|                        | Idoxuridine (topical)    |                           | BCNA Cf 1742                                                |
|                        | Trifluridine (topical)   |                           | BCNA Cf 1743                                                |
| β-Herpes (CMV, HHV-6, HHV-7) | Ganciclovir         | Maribavir                  | CMV423 HDP-CDV (CMX001)                                      |
|                        | Valganciclovir           |                           | ODE-CDV                                                     |
|                        | Cidofovir                |                           | 3-Deaza-HPMPA                                               |
|                        | Foscarnet                |                           |                                                           |
|                        | Fomiviren                |                           |                                                           |
| γ-Herpes (EBV, HHV-8)  | Cidofovir (“off label”)       |                           | North-methanocarbathymidine (N-MCT)                         |
| Virus                        | Compound                              | Approved for medical use | In clinical development | In preclinical evaluation |
|-----------------------------|---------------------------------------|--------------------------|-------------------------|---------------------------|
| Pox (Variola, Vaccinia, Monkeypox, Molluscum contagiosum, orf, ...) | Cidofovir ("off label")              | –                        | HPMPO-DAPy              | HDP-CDV, ODE-CDV          |
|                             |                                       |                          |                         | HDP-HPMPA, ODE-HPMPA      |
|                             |                                       |                          |                         | CI-1033                   |
|                             |                                       |                          |                         | ST-246                    |
|                             |                                       |                          |                         | 5-X-dUrds                 |
|                             |                                       |                          |                         | Pyrazolone-pyrimidine 2′-deoxy-nucleoside chimera |
|                             |                                       |                          |                         | Cyclopentenyl 1,2,3-triazole-4-carboxamide |
| Hepadna (HBV)               | Lamivudine                            |                          | Valtoricitabine          | 3′-Fluoro-2′,3′-dideoxyguanosine |
|                             | Adefovir dipivoxil                     |                          | Clevudine                | Helioxanthin              |
|                             | Entecavir                              |                          |                          |                           |
|                             | Pegylated interferon-α                 |                          |                          |                           |
|                             | Telbivudine                            |                          |                          |                           |
| Retro (HIV)                 | Zidovudine                             | BMS-378806               |                          | Cyclotriazadisulfonamide  |
|                             | Didanosine                             | BMS-488043               |                          | Cyanovirin N              |
|                             | Zalcitabine                            | AMD-3100                 |                          | KRH-1636                  |
|                             | Stavudine                              | SCH-C                    |                          | TAK-779                   |
|                             | Lamivudine                             | Vicriviroc               |                          | TAK-220                   |
|                             | Abacavir                               | Aplaviroc                |                          | TAK-652                   |
|                             | Emtricitabine                          | Maraviroc                |                          | MIV-210                   |

(continued on next page)
| Virus                        | Compound                  | Approved for medical use | In clinical development | In preclinical evaluation |
|-----------------------------|---------------------------|--------------------------|-------------------------|--------------------------|
| Tenofovir disoproxil fumarate| Racivir                   | DOT                      |                         |                          |
| Nevirapine                  | AVX-754                   | 4′-Ed4T                  |                         |                          |
| Delavirdine                 | Reverset                  | PMEO-DAPy                |                         |                          |
| Efavirenz                   | Elvucitabine              | PMPO-DAPy                |                         |                          |
| Saquinavir                  | Alovudine                 | PMDTA                    |                         |                          |
| Ritonavir                   | Amdoxovir                 | PMDTT                    |                         |                          |
| Indinavir                   | Capravirine               | HDP-HPMPA, ODE-HPMPA     |                         |                          |
| Nelfinavir                  | Etravirine                | Thioacarboxanilide UC-781|                         |                          |
| Amprenavir                  | Brecanavir                | Dapivirine               |                         |                          |
| Lopinavir                   | PA-457                    | Rilpivirine              |                         |                          |
| Atazanavir                  | GW678248                  | L-870810                 |                         |                          |
| Fosamprenavir               |                           | L-870812                 |                         |                          |
| Tipranavir                  |                           | GS-9137 (JTK-303)        |                         |                          |
| Darunavir                   |                           | Dihydroxytropolone       |                         |                          |
| Enfuvirtide                 |                           | Pyrimidinyl diketo acid  |                         |                          |
|                            |                           | Indolyl aryl sulfone     |                         |                          |
|                            |                           | Pradimicin A             |                         |                          |
Figure 1. Structural formulae of antiviral compounds.
Figure 1. — Continued.
Figure 1. — Continued.

TAK-220, a CCR5 antagonist, structurally related to TAK-779, which has proved to be a highly potent (orally bioavailable) inhibitor of CCR5-using (R5) HIV-1 strains, and acts synergisti-
Figure 1. — Continued.
cally with other antiretrovirals; TAK-652, another orally bioavailable inhibitor of CCR5-mediated HIV infection.

Noteworthy among the new NRTIs are MIV-210, a prodrug of the NRTI 3′-fluoro-2′,3′-dideoxyguanosine; the thymine dioxolane DOT, another NRTI; 4′-Ed4T (2′,3′-didehydro-3′-deoxy-4′-ethynyl-2′-deoxythymidine), which has favorable oral bioavailability and a unique drug resistance profile, different from that of the other NRTIs. Newly synthesized “phosphonate” analogues include the NtRTIs
6-[2-(phosphonomethoxy)alkoxy]-2,4-diaminopyrimidines PMPO-DAPy, PMEO-DAPy, and 5-substituted derivatives thereof,\textsuperscript{51} and the deoxythreosyl nucleoside phosphonates phosphonomethyldeoxythreosyladenine (PMDTA) and -thymine (PMDTT).\textsuperscript{156} Also alkoxyalkyl i.e. hexadecyloxypropyl (HDP) and octadecyloxyethyl (ODE)] esters of the prototype “phosphonate”, (S)-9-[3-hydroxy-2-(phosphonomethoxy)-
propyl-adenine [HPMPA] have been reported to inhibit HIV-1 replication in vitro at nanomolar concentrations.\(^{77}\)

Among the NNRTIs which have been further pursued for their anti-HIV potential, are thiocarboxanilide UC-781 and dapivirine (TMC-120), both as topical microbicides, and rilpivirine (R-278474), one of the most potent anti-HIV agents ever described;\(^{82}\) GW678248, a novel benzophenone NNRTI,\(^{61,74}\) which has activity at 1 nM against the K103N and Y181C RT HIV-1 mutants associated with clinical resistance to efavirenz and nevirapine, respectively,\(^{133}\) the alkenyl-diarylmethanes
Figure 1. — Continued.

(ADAMS) with metabolically labile methylester moieties replaced by isoxazolone, isoxazole, oxazolone or cyano substituents.54

The polymerase activity of the HIV-1 reverse transcriptase (RT) is entirely dependent on the heterodimeric structure of the enzyme. RT dimerization, therefore, represents a molecular target for the development of new HIV inhibitors; it is the point of attack for the 2′,5′-bis-0-
tert-butyldimethylsilyl-β-D-ribofuranosyl]-3′-spiro-5′′-(4′′-amino-1″,2″-oxathiole-2″,2′″-dioxide)-thymine (TSAO-T) derivatives, a class of compounds originally categorized under the NNRTIs.\textsuperscript{139}

A number of compounds, among which the 1,6-naphthyridine-7-carboxamides L-870,810 and L-870,812, are targeted at the HIV-1 integrase.\textsuperscript{75,76} Novel HIV-1 integrase inhibitors have been derived from quinolone antibiotic.\textsuperscript{136} Phase I/II clinical studies have been undertaken with GS-9137 (JTK-303), the prototype of this class of compounds.\textsuperscript{53} This compound showed an EC\textsubscript{50} of 0.9 nM in an acute HIV-1 infection assay,\textsuperscript{136} and effected a 2 log\textsubscript{10} reduction in viral load in short-term trials in short-term monotherapy trials.\textsuperscript{53} The 3,7-dihydroxytropolones represent an interesting platform for the design of inhibitors of both the reverse transcriptase (and RNase H) as well
Zidovudine
3’-Azido-2’,3’-dideoxythymidine, azidothymidine (AZT)
Retrovir®

Didanosine
2’,3’-Dideoxyinosine (ddl)
Videx®, Videx® EC

Zalcitabine
2’,3’-Dideoxycytidine (ddC)
Hivid®

Stavudine
2’,3’-Didehydro-2’,3’-dideoxythymidine (d4T)
Zerit®

Abacavir
(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol succinate (ABC)
Ziagen®

Figure 1. — Continued.
Figure 1. — Continued.
as the HIV integrase.\textsuperscript{55} Similarly, indolyl aryl sulfone may serve as a platform for the design of new NNRTIs effective against K103N HIV-1 variants.\textsuperscript{20} Recently, diketo acids bearing a nucleobase scaffold have
been described as highly potent HIV integrase inhibitors. The prototype compound, 4-(1,3-dibenzyl-1,2,3,4-tetrahydro-2,4-dioxopyrimidin-5-yl)-2-hydroxy-4-oxo-but-2-enoic acid, exhibited an anti-HIV selectiv-
Lopinavir
combined with ritonavir at 4/1 ratio
Kaletra®

Atazanavir
Reyataz®

Fosamprenavir
Lexiva®, Telzir®

Figure 1. — Continued.
Meanwhile, an HIV vector-based single-cycle assay has been developed which should facilitate the evaluation of potential HIV integrase inhibitors.17

Among the PIs, novel HIV-1 protease inhibitors have been described which were designed specifically to interact with the backbone of HIV protease active site to combat drug resistance,66 and, among the triterpene (betulinic acid) derivatives new potent anti-HIV agents were reported164 to demonstrate a better antiviral profile than the prototype compound PA-457.100

In addition to the aforementioned cyanovirin-N, thiocarboxanilide UC-781 and dapivirine, there are some other compounds that could be further developed as topical (i.e. vaginal) microbicides, namely the aglycons of the glycopeptide antibiotics vancomycin, teicoplanin and eremomycin which specifically interact with the gp120 glycoprotein.126

Also the plant lectins, i.e. *Galanthus* nivalis agglutinin (GNA) and *Hippopaeastrum* hybrid agglutinin (HHA) represent potential candidate anti-
Figure 1. — Continued.
HIV microbicides: they show marked stability at relatively low pH and high temperatures for prolonged time periods, they directly interact with the viral envelope and prevent entry of HIV into its target cells.\textsuperscript{7} Upon prolonged exposure of HIV in cell culture to HHA or GNA, the virus acquires resistance mutations in the gp120 glycoprotein which are predominantly located at the N-glycosylation (asparagine) sites.\textsuperscript{8}

Cyanovirin-N and the plant lectins GNA and HHA can be termed carbohydrate-binding agents (CBAs); due to their carbohydrate-binding properties, they interact with the viral envelope glycoprotein, thereby preventing the HIV entry process. Recently, a non-peptidic benzon-
aphtacene quinone antibiotic, pradimicin A, has been described as a low-molecular-weight CBA that blocks HIV entry by specifically interacting with the mannose moieties of the HIV-1 gp120.⁹
An avenue to be further explored is the combination of different microbicides, such as the NNRTI thiocarboxanilide UC-781 with the cellulose acetate 1,2-benzenedicarboxylate (CAP) viral entry inhibitor, which exhibit synergistic and complementary effects against HIV-1 in-
There is, in addition, no shortage of sulfated and sulfonated polymers (starting off with suramin, the first polysulfonate ever shown to be active against HIV) which could be considered as topical anti-HIV microbicides.

RNA interference (RNAi) may be considered a new powerful tool for intracellular immunization against HIV-1 infection. It has been demonstrated in short-term assays that HIV-1 replication can be inhibited by siRNAs directed against viral targets (i.e. *rev*) or cellular targets (i.e. CCR5). As to the viral targets, siRNAs targeting conserved *gag*, *pol*, *int*, *vpu* regions or *gp41*, *tat*, *rev* or *nef* were shown to inhibit virus production. Although targeting single HIV-1 sequences with siRNAs can result in strong inhibition of viral replication, it is likely followed by the escape of mutated viral variants. Therefore, antiviral approaches involving RNAi should be used in a combined fashion so as to prevent emergence of resistant viruses.
It is, furthermore, worth investigating whether RNAi can be harnessed for use in microbicides. As described above, an siRNA-based microbicide has been shown to protect mice from lethal HSV-2 in-
Extension of these results to the design of an HIV microbicide would also require demonstrating silencing in resident tissue macrophages, dendritic cells and T cells. Further considering the requirement of combining siRNAs that target multiple viral genes so as to cover viral sequence diversity and to prevent potential escape mutation, the development of an effective siRNA-based HIV microbicide may seem as a challenging task.

**XII. CONCLUSION**

About forty compounds are registered as antiviral drugs, at least half of which are used to treat HIV infections. An even greater number of compounds are under clinical or preclinical development, with again, as many targeting HIV as all the other viruses taken together. This implies that HIV, since its advent, has remained the main stay
(H₂N)Leu—Gly—Lys—Phe—Ser—Gln—Thr—Cys—Tyr—Asn—Ser—Ala—
— Ile—Gln—Gly—Ser—Val—Leu—Thr—Ser—Thr—Cys—Glu—Arg—Thr—Asn—Gly—Gly—Tyr—Asn—Thr—Ser—
— Ser—Ile—Asp—Leu—Asn—Ser—Val—Ile—Glu—Asn—Val—Asp—Gly—Ser—Leu—Lys—Trp—Gln—Pro—Ser—
— Asn—Phe—Ile—Glu—Thr—Cys—Arg—Asn—Thr—Gln—Leu—Ala—Gly—Ser—Ser—Glu—Leu—Ala—Ala—Glu—
—Cys—Lys—Thr—Arg—Ala—Gln—Gln—Phe—Val—Ser—Thr—Lys—Ile—Asn—Leu—Asp—Asp—His—Ile—Ala—
— Asn—Ile—Asp—Gly—Thr—Leu—Iys—Tyr—Glu(COOH)

Cyanovirin-N

*Figure 1. — Continued.*
Figure 1. — Continued.
Antiviral agents can, as guided by the anti-HIV agents as examples, be divided in roughly five categories:

(i) nucleoside analogues,
(ii) nucleotide analogues (or acyclic nucleoside phosphonates),
(iii) non-nucleoside analogues,
(iv) protease inhibitors, and
(v) virus–cell fusion inhibitors.

Molecular targets are for (i) and (ii) the viral DNA polymerase (whether DNA-dependent as in the case of herpesviruses, or RNA-dependent as in the case of HIV or HBV); for (iii) RNA-dependent DNA polymerase (reverse transcriptase), associated with HIV, or RNA-dependent RNA polymerase (RNA replicase) associated with HCV; for (iv) the proteases associated with HIV and HCV; and for (v) the fusion
process of HIV (and, potentially, other viruses such as the SARS coronavirus and RSV). Antiviral agents may also exert their antiviral effects through an interaction with cellular targets such as IMP dehydrogenase (ribavirin) and SAH hydrolase (3-deazaadenosine A). The latter
enzymes are essential for viral RNA synthesis (through the supply of GTP) and viral mRNA maturation (through 5’-capping), respectively. Finally, interferons (now generally provided in their pegylated form)
may be advocated in the therapy of those viral infections (actually, HBV and HCV; prospectively, Coxsackie B, SARS, . . .) that, as yet, cannot be sufficiently curbed by other therapeutic measures.

**ACKNOWLEDGEMENTS**

I thank Mrs. Christiane Callebaut for her invaluable editorial assistance.

**REFERENCES**

1. G. Andrei, R. Snoeck, M. Vandeputte, E. De Clercq, Activities of various compounds against murine and primate polyomaviruses, *Antimicrob. Agents Chemother.* 41 (1997) 587–593.
DNA VIRUSES AND RETROVIRUSES

2. G. Andrei, R. Sienaert, C. McGuigan, E. De Clercq, J. Balzarini, R. Snoeck, Susceptibilities of several clinical varicella-zoster virus (VZV) isolates and drug-resistant VZV strains to bicyclic furano pyrimidine nucleosides, Antimicrob. Agents Chemother. 49 (2005) 1081–1086.

3. G. Andrei, D.B. Gammon, P. Fiten, E. De Clercq, G. Opdenakker, R. Snoeck, D.H. Evans, Cidofovir resistance in vaccinia virus is linked to diminished virulence in mice, J. Virol. 80 (2006) 9391–9401.

4. H.J. Arteaga, J. Hinkula, I. van Dijk-Hard, M.S. Dilber, B. Wahren, B. Christenson, A.J. Mohamed, C.I. Smith, Choosing CCR5 or Rev siRNA in HIV-1, Nature Biotechnol. 21 (2003) 230–231.

5. M. Baba, O. Nishimura, N. Kanzaki, M. Okamoto, H. Sawada, Y. Iizawa, M. Siraiishi, Y. Aramaki, K. Okonogi, Y. Ogawa, K. Meguro, M. Fujino, A small-molecule, nonpeptide CCR5 antagonist with highly potent and selective anti-HIV-1 activity, Proc. Natl. Acad. Sci. USA 96 (1999) 5698–5703.

6. M. Baba, K. Takashima, H. Miyake, N. Kanzaki, K. Teshima, X. Wang, M. Shiraishi, Y. Iizawa, TAK-652 inhibits CCR5-mediated human immunodeficiency virus type 1 infection in vitro and has favorable pharmacokinetics in humans, Antimicrob. Agents Chemother. 49 (2005) 4584–4591.

7. J. Balzarini, S. Hatse, K. Vermeire, K. Princen, S. Aquaro, C.F. Perno, E. De Clercq, H. Egberink, G. Vandemootere, W. Peumans, E. Van Damme, D. Schols, Mannose-specific plant lectins from the Amaryllidaceae family qualify as efficient microbicides for prevention of human immunodeficiency virus infection, Antimicrob. Agents Chemother. 48 (2004) 3858–3870.

8. J. Balzarini, K. Van Laethem, S. Hatse, K. Vermeire, E. De Clercq, W. Peumans, E. Van Damme, A.M. Vandamme, A. Bolmstedt, D. Schols, Profile of resistance of human immunodeficiency virus to mannose-specific plant lectins, J. Virol. 78 (2004) 10617–10627.

9. J. Balzarini, K. Van Laethem, D. Daelemans, S. Hatse, A. Bugatti, M. Rusnati, Y. Igarashi, T. Oki, D. Schols, Pradimicin A, a carbohydrate-binding nonpeptidic lead compound for treatment of infections with viruses with highly glycosylated envelopes, such as human immunodeficiency virus, J. Virol. 81 (2007) 362–373.

10. J.R. Beadle, C. Hartline, K.A. Aldern, N. Rodriguez, E. Harden, E.R. Kern, K.Y. Hostetler, Alkoxylalkyl esters of cidofovir and cyclic cidofovir exhibit multiple-log enhancement of antiviral activity against cytomegalovirus and herpesvirus replication in vitro, Antimicrob. Agents Chemother. 46 (2002) 2381–2386.

11. J.R. Beadle, W.B. Wan, S.L. Ciesla, K.A. Keith, C. Hartline, E.R. Kern, K.Y. Hostetler, Synthesis and antiviral evaluation of alkoxylalkyl derivatives of 9-(3-hydroxy-2-phosphonomethoxypropyl)adenine against cytomegalovirus and orthopoxviruses, J. Med. Chem. 49 (2006) 2010–2015.

12. Y. Benhamou, H. Fleury, P. Trimolet, I. Pellegrin, R. Uribinelli, C. Katlama, W. Rozenbaum, G. Le Teuff, A. Trylesinski, C. Pikitay, Anti-hepatitis B virus efficacy of tenofovir disoproxil fumarate in HIV-infected patients, Hepatology 43 (2006) 548–555.

13. U.A. Betz, R. Fischer, G. Kleymann, M. Hendrix, H. Rübsamen-Waigmann, Potent in vivo antiviral activity of the herpes simplex virus primase-helicase inhibitor BAY 57-1293, Antimicrob. Agents Chemother. 46 (2002) 1766–1772.

14. K.K. Biron, Antiviral drugs for cytomegalovirus diseases, Antiviral Res. 71 (2006) 154–163.

15. K.K. Biron, R.J. Harvey, S.C. Chamberlain, S.S. Good, A.A. Smith 3rd, M.G. Davis, C.L. Talarico, W.H. Miller, R. Ferris, R.E. Dornsife, S.C. Stanat, J.C. Drach,
L.B. Townsend, G.W. Koszalka, Potent and selective inhibition of human cytomegalovirus replication by 1263W94, a benzimidazole L-riboside with a unique mode of action, *Antimicrob. Agents Chemother.* 46 (2002) 2365–2372.

16. S. Biswas, L. Jennens, H.J. Field, The helicase primase inhibitor, BAY 57-1293 shows potent therapeutic antiviral activity superior to famciclovir in BALB/c mice infected with herpes simplex virus type 1, *Antiviral Res.*, in press.

17. R. Bona, M. Andreotti, V. Buffa, P. Leone, C.M. Galluzzo, R. Amici, L. Palmisano, M.G. Mancini, Z. Michelini, R. Di Santo, R. Costi, A. Roux, Y. Pommier, C. Marchand, S. Vella, A. Cara, Development of a human immunodeficiency virus vector-based single-cycle assay for evaluation of anti-integrase compounds, *Antimicrob. Agents Chemother.* 50 (2006) 3407–3417.

18. M.R. Boyd, K.R. Gustafson, J.B. McMahon, R.H. Shoemaker, B.R. O'Keefe, T. Mori, R.J. Gulakowski, L. Wu, M.I. Rivera, C.M. Laurencot, M.J. Currens, J.H. Cardellina 2nd, R.W. Buckheit Jr, P.L. Nara, L.K. Pannell, R.C. Sower 2nd, L.E. Henderson, Discovery of cyanovirin-N, a novel human immunodeficiency virus-inactivating protein that binds viral surface envelope glycoprotein gp120: potential applications to microbicide development, *Antimicrob. Agents Chemother.* 41 (1997) 1521–1530.

19. R.M. Bulller, G. Owens, J. Schriewer, L. Melman, J.R. Beadle, K.Y. Hostetler, Efficacy of oral active ether lipid analogs of cidofovir in a lethal mousepox model, *Virology* 318 (2004) 474–481.

20. R. Cancio, R. Silvestri, R. Ragno, M. Artico, G. De Martino, G. La Regina, E. Crespan, S. Zanoli, U. Hubscher, S. Spadari, G. Maga, High potency of indolyl aryl sulfone nonnucleoside inhibitors towards drug-resistant human immunodeficiency virus type 1 reverse transcriptase mutants is due to selective targeting of different mechanistic forms of the enzyme, *Antimicrob. Agents Chemother.* 49 (2005) 4546–4554.

21. L.-J. Chang, X. Liu, J. He, Lentiviral siRNAs targeting multiple highly conserved RNA sequences of human immunodeficiency virus type 1, *Gene Ther.* 12 (2005) 1133–1144.

22. T-T. Chang, R.G. Gash, R. de Man, A. Gadano, J. Sollano, Y.C. Chao, A.S. Lok, K.H. Han, Z. Goodman, J. Zhu, A. Cross, D. DeHertogh, R. Wilber, R. Colombo, D. Apelean, A comparison of entecavir and lamivudine for HBeAg-positive chronic hepatitis B, *N. Engl. J. Med.* 354 (2006) 1001–1010.

23. Y.-C. Cheng, C.-X. Ying, C.-H. Leung, Y. Li, New targets and inhibitors of HBV replication to combat drug resistance, *J. Clin. Virol.* 34 (Suppl. 1) (2005) S147–S150.

24. J.H. Cho, D.L. Bernard, R.W. Sidwell, E.R. Kern, C.K. Chu, Synthesis of cyclopentenyl carbocyclic nucleosides as potential antiviral agents against orthopoxviruses and SARS, *J. Med. Chem.* 49 (2006) 1140–1148.

25. S. Chou, G.I. Marousek, Maribavir antagonizes the antiviral action of ganciclovir on human cytomegalovirus, *Antimicrob. Agents Chemother.* 50 (2006) 3470–3472.

26. S. Chou, L.C. Van Wechel, G.I. Marousek, Effect of cell culture conditions on the anticytomegalovirus activity of maribavir, *Antimicrob. Agents Chemother.* 50 (2006) 2557–2559.

27. C.K. Chu, V. Yadav, Y.H. Chong, R.F. Schinazi, Anti-HIV activity of (−)-(2R,4R)-1-(2-hydroxymethyl-1,3-dioxolan-4-yl)-thymine against drug-resistant HIV-1 mutants and studies of its molecular mechanism, *J. Med. Chem.* 48 (2005) 3949–3952.

28. S.L. Ciesla, J. Trahan, W.B. Wan, J.R. Beadle, K.A. Aldern, G.R. Painter, K.Y. Hostetler, Esterification of cidofovir with alkoxysilanes increases oral bioavailability and diminishes drug accumulation in kidney, *Antiviral Res.* 59 (2003) 165–171.
29. J.J. Crute, T. Tsurumi, L. Zhu, S.K. Weller, P.D. Olivo, M.D. Challberg, E.S. Mocarski, I.R. Lehman, Herpes simplex virus 1 helicase–primase: a complex of three herpes-encoded gene products, Proc. Natl. Acad. Sci. USA 86 (1989) 2186–2189.

30. J.J. Crute, C.A. Grygon, K.D. Hargrave, B. Simoneau, A.M. Faucher, G. Bolger, P. Kibler, M. Liuzzi, M.G. Cordingly, Herpes simplex virus helicase–primase inhibitors are active in animal models of human disease, Nature Med. 8 (2002) 386–391.

31. F. Dal Pozzo, G. Andrei, A. Holý, J. Van Den Oord, A. Scaglariini, E. De Clercq, R. Snoeck, Activities of acyclic nucleoside phosphonates against Orf virus in human and ovine cell monolayers and organotypic ovine raft cultures, Antimicrob. Agents Chemother. 49 (2005) 4843–4852.

32. A.T. Das, T.R. Brummelkamp, E.M. Westerhout, M. Vink, M. Madiredjo, R. Bernards, B. Berkhout, Human immunodeficiency virus type 1 escapes from RNA interference-mediated inhibition, J. Virol. 78 (2004) 2601–2605.

33. R.S. Dave, R.J. Pomerantz, Antiviral effects of human immunodeficiency virus type 1-specific small interfering RNAs against targets conserved in select neurotropic viral strains, J. Virol. 78 (2004) 13687–13696.

34. R.S. Dave, J.P. McGettigan, T. Qureshi, M.J. Schnell, G. Nunnari, R.J. Pomerantz, siRNA targeting vaccinia virus double-stranded RNA binding protein [E3L] exerts potent antiviral effects, Virology 348 (2006) 489–497.

35. L. De Bolle, G. Andrei, R. Snoeck, Y. Zhang, A. Van Lommel, M. Otto, A. Bousseau, C. Roy, E. De Clercq, L. Naesens, Potent, selective and cell-mediated inhibition of human herpesvirus 6 at an early stage of viral replication by the non-nucleoside compound CMV423, Biochem. Pharmacol. 67 (2004) 325–336.

36. L. De Bolle, L. Naesens, E. De Clercq, Update on human herpesvirus 6 biology, clinical features, and therapy, Clin. Microbiol. Rev. 18 (2005) 217–245.

37. E. De Clercq, Vaccinia virus inhibitors as a paradigm for the chemotherapy of poxvirus infections, Clin. Microbiol. Rev. 14 (2001) 382–397.

38. E. De Clercq, Cidofovir in the treatment of poxvirus infections, Antiviral Res. 55 (2002) 1–13.

39. E. De Clercq, Clinical potential of acyclic nucleoside phosphonates cidofovir, adefovir, and tenofovir in treatment of DNA virus and retrovirus infections, Clin. Microbiol. Rev. 16 (2003) 569–596.

40. E. De Clercq, Highly potent and selective inhibition of varicella-zoster virus replication by bicyclic furo[2,3-d]pyrimidine nucleoside analogues, Med. Res. Rev. 23 (2003) 253–274.

41. E. De Clercq, New inhibitors of HCMV (human cytomegalovirus) on the horizon, J. Antimicrob. Chemother. 51 (2003) 1079–1083.

42. E. De Clercq, Potential of acyclic nucleoside phosphonates in the treatment of DNA virus and retrovirus infections, Expert Rev. Anti-infect. Ther. 1 (2003) 21–43.

43. E. De Clercq, The bicyclam AMD3100 story, Nature Rev. Drug Discovery 2 (2003) 581–587.

44. E. De Clercq, Antiviral drugs in current clinical use, J. Clin. Virol. 30 (2004) 115–133.

45. E. De Clercq, Emerging anti-HIV drugs, Expert Opin. Emerging Drugs 10 (2005) 241–274.

46. E. De Clercq, H.J. Field, Antiviral prodrugs—the development of successful prodrug strategies for antiviral chemotherapy, Brit. J. Pharmacol. 147 (2005) 1–11.

47. E. De Clercq, L. Naesens, In search of effective anti-HHV-6 agents, J. Clin. Virol. (Suppl.) (2006) S82–S86.
48. E. De Clercq, J. Neyts, Therapeutic potential of nucleoside/nucleotide analogues against poxvirus infections, *Rev. Med. Virol.* 14 (2004) 289–300.
49. E. De Clercq, G. Andrei, R. Snoeck, L. De Bolle, L. Naesens, B. Degreve, J. Balzarini, Y. Zhang, D. Schols, P. Leyssen, C. Ying, J. Neyts, Acyclic/carbocyclic guanosine analogues as anti-herpesvirus agents, *Nucleosides, Nucleotides & Nucleic Acids* 20 (2001) 271–285.
50. E. De Clercq, L. Naesens, L. De Bolle, D. Schols, Y. Zhang, J. Neyts, Antiviral agents active against human herpesviruses HHV-6, HHV-7, HHV-7 and HHV-8, *Rev. Med. Virol.* 11 (2001) 381–395.
51. E. De Clercq, G. Andrei, J. Balzarini, P. Leyssen, L. Naesens, J. Neyts, C. Pannecouque, R. Snoeck, C. Ying, D. Hocková, A. Holý, Antiviral potential of a new generation of acyclic nucleoside phosphonates, the 6-[2-(phosphonomethoxy)alkoxy]-2,4-diaminopyrimidines, *Nucleosides, Nucleotides & Nucleic Acids* 24 (2005) 331–341.
52. S. De Meyer, H. Azijn, D. Surleraux, D. Johmans, A. Tahri, R. Pauwels, M.-P. Wigerinck, P. de Béthune, TMC114, a novel human immunodeficiency virus type 1 protease inhibitor active against protease inhibitor-resistant viruses, including a broad range of clinical isolates, *Antimicrob. Agents Chemother.* 49 (2005) 2314–2321.
53. E. DeJesus, D. Berger, M. Markowitz, C. Cohen, T. Hawkins, P. Ruane, R. Elion, C. Farthing, L. Zhong, A.K. Cheng, D. McColl, B.P. Kearney, Antiviral activity, pharmacokinetics, and dose response of the HIV-1 integrase inhibitor GS-9137 (JTK-303) in treatment-native and treatment-experienced patients, *J. Acquir. Immune Defic. Syndr.* 43 (2006) 1–5.
54. B.-L. Deng, T.L. Hartman, R.W. Buckheit Jr, C. Pannecouque, E. De Clercq, M. Cushman, Replacement of the metabolically labile methyl esters in the alkenyl-diarylmethane series of non-nucleoside reverse transcriptase inhibitors with isoxazolone, isoxazole, oxazolone, or cyano substituents, *J. Med. Chem.* 49 (2006) 5316–5323.
55. J. Didierjean, C. Isel, F. Querré, J.F. Mouscadet, A.M. Aubertin, J.Y. Valnot, S.R. Piettre, R. Marquet, Inhibition of human immunodeficiency virus type 1 reverse transcriptase, RNase H, and integrase activities by hydroxypolones, *Antimicrob. Agents Chemother.* 49 (2005) 4884–4894.
56. P. Dorr, M. Westby, S. Dobbs, Maraviroc (UK-427,857), a potent, orally bioavailable, and selective small-molecule inhibitor of chemokine receptor CCR5 with broad-spectrum anti-human immunodeficiency virus type 1 activity, *Antimicrob. Agents Chemother.* 49 (2005) 4721–4732.
57. J. Duan, M. Liuzzi, W. Paris, F. Liard, A. Browne, N. Dansereau, B. Simonneau, A.-M. Faucher, M.G. Cordingley, Oral bioavailability and in vivo efficacy of the helicase–primase inhibitor BILS 45 BS against acyclovir-resistant herpes simplex virus type 1, *Antimicrob. Agents Chemother.* 47 (2003) 1798–1804.
58. X. Fan, X. Zhang, L. Zhou, K.A. Keith, E.R. Kern, P.F. Torrence, 5-(Di-methoxymethyl)-2′-deoxyuridine: a novel gem diether nucleoside with anti-orthopoxvirus activity, *J. Med. Chem.* 49 (2006) 3377–3382.
59. X. Fan, X. Zhang, L. Zhou, K.A. Keith, E.R. Kern, P.F. Torrence, A pyrimidine-pyrazolone nucleoside chimera with potent in vitro anti-orthopoxvirus activity, *Bioorg. Med. Chem. Lett.* 16 (2006) 3224–3228.
60. A.M. Faucher, P.W. White, C. Brochu, C. Grand-Maitre, J. Rancourt, G. Fzal, Discovery of small-molecule inhibitors of the ATPase activity of human papillomavirus E1 helicase, *J. Med. Chem.* 47 (2004) 18–21.
DNA VIRUSES AND RETROVIRUSES

61. R.G. Ferris, R.J. Hazen, G.B. Roberts, M.H. St. Clair, J.H. Chan, K.R. Romines, G.A. Freeman, J.H. Tidwell, L.T. Schaller, J.R. Cowan, S.A. Short, K.L. Weaver, D.W. Selleseth, K.R. Moniri, L.R. Boone, Antiviral activity of GW678248, a novel benzophenone nonnucleoside reverse transcriptase inhibitor, Antimicrob. Agents Chemother. 49 (2005) 4046–4051.

62. N. Flomenberg, S.M. Devine, J.F. DiPersio, J.L. Liesveld, J.M. McCarty, S.D. Rowley, K. Vesole, D.H. Badel, G. Calandra, The use of AMD3100 plus G-CSF for autologous hematopoietic progenitor cell mobilization is superior to G-CSF alone, Blood 106 (2005) 1867–1874.

63. S.L. Ford, Y.S. Reddy, M.T. Anderson, S.C. Murray, P. Fernandez, D.S. Stein, M.A. Johnson, Single-dose safety and pharmacokinetics of brecanavir, a novel human immunodeficiency virus protease inhibitor, Antimicrob. Agents Chemother. 50 (2006) 2201–2206.

64. S.K. Fung, P. Andreone, S.H. Han, K.R. Reddy, A. Regev, E.B. Keeffe, M. Hussain, C. Cursaro, P. Richtmyer, J.A. Marrero, A.S.F. Lok, Adefovir-resistant hepatitis B can be associated with viral rebound and hepatic decompensation, J. Hepatol. 43 (2005) 937–943.

65. S.K. Fung, H.B. Chae, R.J. Fontana, H. Conjeevaram, J. Marrero, K. Oberhelman, M. Hussain, A.S.F. Lok, Virologic response and resistance to adefovir in patients with chronic hepatitis B, J. Hepatol. 44 (2006) 283–290.

66. A.K. Ghosh, P.R. Sridhar, S. Leshchenko, A.K. Hussain, J. Li, A.Y. Kovalevsky, D.E. Walters, J.E. Widekind, V. Grum-Tokars, D. Das, Y. Koh, K. Maeda, H. Gatanaga, I.T. Weber, H. Mitsuya, Structure-based design of novel HIV-1 protease inhibitors to combat drug resistance, J. Med. Chem. 49 (2006) 5252–5261.

67. H. Giladi, M. Ketzinel-Gilad, L. Rivkin, Y. Felig, O. Nussbaum, E. Galun, Small interfering RNA inhibits hepatitis B virus replication in mice, Mol. Ther. 8 (2003) 769–776.

68. B. Golankiewicz, T. Ostrowski, Tricyclic nucleoside analogues as antitherpes agents, Antiviral Res. 71 (2006) 134–140.

69. Z. Gu, B. Allard, J.M. de Muys, L. Lippens, R.F. Rando, N. Nguyen-Ba, C. Ren, P. McKenna, D.L. Taylor, R.C. Bethell, In vitro antiretroviral activity and in vitro toxicity profile of SPD754, a new deoxycytidine nucleoside reverse transcriptase inhibitor for treatment of human immunodeficiency virus infection, Antimicrob. Agents Chemother. 50 (2006) 625–631.

70. S.J. Hadziyannis, N.C. Tassopoulos, E.J. Heathcote, T.T. Chang, G. Kitis, M. Rizzetto, P. Marcellin, S.G. Lim, Z. Goodman, M.S. Wulfschohn, S. Xiong, J. Fry, C.L. Brosgart, Adefovir dipivoxil for the treatment of hepatitis B e antigen-negative chronic hepatitis B, N. Engl. J. Med. 348 (2003) 800–807.

71. S.J. Hadziyannis, N.C. Tassopoulos, E.J. Heathcote, T.T. Chang, G. Kitis, M. Rizzetto, P. Marcellin, S.G. Lim, Z. Goodman, J. Ma, S. Arterburn, S. Xiong, G. Currie, C.L. Brosgart, Long-term therapy with adefovir dipivoxil for HBsAg-negative chronic hepatitis B, N. Engl. J. Med. 352 (2005) 2673–2681.

72. Y.X. Han, R. Xue, W. Zhao, Z.X. Zhou, H.S. Li, J.N. Chen, Y.L. Chen, X.H. Wang, Y.H. Li, Y.W. Wu, X.F. You, L.X. Zhao, J.D. Jiang, Antiviral therapeutic efficacy of foscarnet in hepatitis B virus infection, Antiviral Res. 68 (2005) 147–153.

73. C.B. Hartline, K.M. Gustin, W.B. Wan, S.L. Ciesla, J.R. Beadle, K.Y. Hostetler, E.R. Kern, Ether lipid-ester prodrugs of acyclic nucleoside phosphonates: activity against adenovirus replication in vitro, J. Infect. Dis. 191 (2005) 396–399.

74. R.J. Hazen, R.J. Harvey, M.H. St. Clair, R.G. Ferris, G.A. Freeman, J.H. Tidwell, L.T. Schaller, J.R. Cowan, S.A. Short, K.R. Romines, J.H. Chan, L.R. Boone, Anti-
human immunodeficiency virus type 1 activity of the nonnucleoside reverse transcriptase inhibitor GW678248 in combination with other antiretrovirals against clinical isolate viruses and in vitro selection for resistance, *Antimicrob. Agents Chemother.* 49 (2005) 4465–4473.

75. D.J. Hazuda, N.J. Anthony, R.P. Gomez, S.M. Joly, J.S. Wai, L. Zhuang, T.E. Fisher, M. Embrey, J.P. Guare Jr, M.S. Egbertson, J.P. Vaca, J.R. Huff, P.J. Felock, M.V. Witmer, K.A. Stillmock, R. Danovich, J. Grobler, M.D. Miller, A.S. Espeseth, L. Jin, I.W. Chen, J.H. Lin, K. Kassahun, J.D. Ellis, B.K. Wong, W. Xu, P.G. Pearson, W.A. Schleif, R. Cortese, E. Emini, V. Summa, M.K. Holloway, S.D. Young, A naphthyridine carboxamide provides evidence for discordant resistance between mechanistically identical inhibitors of HIV-1 integrase, *Proc. Natl. Acad. Sci. USA* 101 (2004) 11233–11238.

76. D.J. Hazuda, S.D. Young, J.P. Guare, N.J. Anthony, R.P. Gomez, J.S. Wai, J.P. Vaca, L. Handt, S.L. Motzel, H.J. Klein, G. Dornadula, R.M. Danovich, M.V. Witmer, K.A. Wilson, L. Tussey, W.A. Schleif, L.S. Gabryelski, L. Jin, M.D. Miller, D.R. Casimiro, E.A. Emini, J.W. Shiver, Integrase inhibitors and cellular immunity suppress retroviral replication in rhesus macaques, *Science* 305 (2004) 528–532.

77. K.Y. Hostetler, K.A. Aldern, W.B. Wan, S.L. Ciesla, J.R. Beadle, Alkoxyalkyl esters of (S)-9-[3-hydroxy-2-(phosphonomethoxy)propyl]adenine are potent inhibitors of the replication of wild-type and drug-resistant human immunodeficiency virus type 1 in vitro, *Antimicrob. Agents Chemother.* 50 (2006) 2044–2049.

78. R. Hu, L. Li, B. Degreve, G.E. Dutschman, W. Lam, Y.-C. Cheng, Behavior of thymidylate kinase toward monophosphate metabolites and its role in the metabolism of 1-(2'-deoxy-2'-fluoro-beta-L-arabinofuranosyl)-5-methyluracil (Clevudine) and 2',3'-didehydro-2',3'-dideoxythymidine in cells, *Antimicrob. Agents Chemother.* 49 (2005) 2044–2049.

79. K. Ichiyama, S. Yokoyama-Kumakura, Y. Tanaka, R. Tanaka, K. Hirose, K. Bannai, T. Edamatsu, M. Yanaka, Y. Niitani, N. Miyano-Kurosaki, H. Takaku, Y. Koyanagi, N. Yamamoto, A duodenally absorbable CXC chemokine receptor 4 antagonist, KRH-1636, exhibits a potent and selective anti-HIV-1 activity, *Proc. Natl. Acad. Sci. USA* 100 (2003) 4185–4190.

80. A.-C. Jacquard, M.-N. Brunelle, C. Pichoud, D. Durantel, S. Carrouee-Durantel, C. Trépo, F. Zoulim, In vitro characterization of the anti-hepatitis B virus activity and cross-resistance profile of 2',3'-dideoxy-3'-fluoroguanosine, *Antimicrob. Agents Chemother.* 50 (2006) 955–961.

81. H.L.A. Janssen, M. van Zonneveld, H. Senturk, S. Zeuzem, U.S. Akarca, Y. Cakaloglu, C. Simon, T.M. So, G. Gerken, R.A. de Man, H.G. Niesters, P. Zondervan, B. Hansen, S.W. Schalm, Pegylated interferon alfa-2b alone or in combination with lamivudine for HBeAg-positive chronic hepatitis B: a randomised trial, *Lancet* 365 (2005) 123–129.

82. P.A. Janssen, P.J. Lewi, E. Arnold, F. Daeyaert, M. de Jonge, J. Heeres, L. Koymans, M. Vinkers, J. Guillemont, E. Pasquier, M. Kukla, D. Loduvici, K. Andries, M.-P. de Béthune, R. Pauwels, K. Das, A.D. Clark Jr, Y.V. Frenkel, S.H. Hughes, B. Medaer, F. De Knaep, H. Bohets, F. De Clerck, A. Lampo, S. Williams, P. Stoffels, In search of a novel anti-HIV drug: multidisciplinary coordination in the discovery of 4-[[4-[[1E]-2-cyanoethyl]1-2,6-dimethylphenyl]amino]-2- pyrimidinyl]amino]benzonitrile (R278474, rilpivirine), *J. Med. Chem.* 48 (2005) 1901–1909.

83. E.R. Kern, C. Hartline, E. Harden, K. Keith, N. Rodriguez, J.R. Beadle, K.Y. Hostetler, Enhanced inhibition of orthopoxvirus replication in vitro by
alkoxyalkyl esters of cidofovir and cyclic cidofovir, Antimicrob. Agents Chemother. 46 (2002) 991–995.

84. E.R. Kern, D.J. Bidanset, C.B. Hartline, Z. Yan, J. Zemlicka, D.C. Quenelle, Oral activity of a methylene cyclopropane analog, cyclopropavir, in animal models for cytomegalovirus infections, Antimicrob. Agents Chemother. 48 (2004) 4745–4753.

85. E.R. Kern, N.L. Kushner, C.B. Hartline, S.L. Williams-Aziz, E.A. Harden, S. Zhou, J. Zemlicka, M.N. Prichard, In vitro activity and mechanism of action of methylene cyclopropane analogs of nucleosides against herpesvirus replication, Antimicrob. Agents Chemther. 49 (2005) 1039–1045.

86. C. Klein, C.T. Bock, H. Wedemeyer, T. Wüstefeld, S. Locarnini, H.P. Dienes, S. Kubicka, M.P. Manns, C. Trautwein, Inhibition of hepatitis B virus replication in vivo by nucleoside analogues and siRNA, Gastroenterology 125 (2003) 9–18.

87. G. Kleymann, R. Fischer, U.A. Betz, M. Hendrix, W. Bender, G. Schneider, U. Handke, P. Eckenberg, G. Hewlett, V. Pevzner, J. Baumeister, O. Weber, K. Henninger, J. Keldenich, A. Jensen, J. Kolb, U. Bach, A. Popp, J. Maben, I. Frappa, D. Haebich, O. Lockhoff, H. Rübsamen-Waigmann, New helicase–primase inhibitors as drug candidates for the treatment of herpes simplex disease, Nature Med. 8 (2002) 392–398.

88. R.S. Kornbluth, D.F. Smee, R.W. Sidwell, V. Snarsky, D.H. Evans, K.Y. Hostetler, Mutations in the E9L polymerase gene of cidofovir-resistant vaccinia virus strain WR are associated with the drug resistance phenotype, Antimicrob. Agents Chemother. 50 (2006) 4038–4043.

89. G.W. Koszalka, N.W. Johnson, S.S. Good, L. Boyd, S.C. Chamberlain, L.B. Townsend, J.C. Drach, K.K. Biron, Preclinical and toxicology studies of 1263W94, a potent and selective inhibitor of human cytomegalovirus replication, Antimicrob. Agents Chemother. 46 (2002) 2373–2380.

90. P.M. Krosky, M.C. Baek, D.M. Coen, The human cytomegalovirus UL97 protein kinase, an antiviral drug target, is required at the stage of nuclear egress, J. Virol. 77 (2003) 905–914.

91. C.L. Lai, M. Rosmawati, J. Lao, F.H. Van Vlierberghhe, H. Anderson, N. Thomas, D. Dehertogh, Entecavir is superior to lamivudine in reducing hepatitis B virus DNA in patients with chronic hepatitis B infection, Gastroenterology 123 (2002) 1831–1838.

92. C.-L. Lai, D. Shouval, A.S. Lok, T.T. Chang, H. Cheinquer, Z. Goodman, D. Dehertogh, R. Wilber, R.C. Zink, A. Cross, R. Colombo, L. Fernandes, Entecavir versus lamivudine for patients with HBeAg-negative chronic hepatitis B, N. Engl. J. Med. 354 (2006) 1011–1020.

93. J.P. Lalezari, J.A. Aberg, L.H. Wang, M.B. Wire, R. Miner, W. Snowden, C.L. Talarico, S. Shaw, M.A. Jacobson, W.L. Drew, Phase I dose escalation trial evaluating the pharmacokinetics, anti-cytomegalovirus (HCMV) activity, and safety of 1263W94 in human immunodeficiency virus-infected men with asymptomatic HCMV shedding, Antimicrob. Agents Chemother. 46 (2002) 2969–2976.

94. P. Lampertico, M. Viganò, E. Manenti, M. Iavarone, G. Lunghi, M. Colombo, Adefovir rapidly suppresses hepatitis B in HBeAg-negative patients developing genotypic resistance to lamivudine, Hepatology 42 (2005) 1414–1419.

95. I. Lebeau, G. Andrei, F. Dal Pozzo, J.R. Beadle, K.Y. Hostetler, E. De Clercq, J. van den Oord, R. Snoeck, Activities of alkoxyalkyl esters of cidofovir (CDV), cyclic CDV, and (S)-9-(3-hydroxy-2-phosphonylmethoxypropyl)adenine against orthopoxviruses in cell monolayers and in organotypic cultures, Antimicrob. Agents Chemother. 50 (2006) 2525–2529.
96. H.-S. Lee, Y.-H. Chung, K. Lee, K.S. Byun, S.W. Paik, J.-Y. Han, K. Yoo, H.-W. Yoo, J.H. Lee, B.C. Yoo, A 12-week clevudine therapy showed potent and durable antiviral activity in HBeAg-positive chronic hepatitis B, Hepatology 43 (2006) 982–988.

97. N.S. Lee, T. Dohjima, G. Bauer, M.J. Li, H. Li, A. Ehsani, P. Salvaterra, J. Rossi, Expression of small interfering RNAs targeted against HIV-1 rev transcripts in human cells, Nature Biotechnol. 20 (2002) 500–505.

98. Y.-S. Lee, D.J. Suh, Y.-S. Lim, S.W. Jung, K.M. Kim, H.C. Lee, Y.-H. Chung, Y.S. Lee, W. Yoo, S.-O. Kim, Increased risk of adefovir resistance in patients with lamivudine-resistant chronic hepatitis B after 48 weeks of adefovir dipivoxil monotherapy, Hepatology 43 (2006) 1385–1391.

99. S. Levine, D. Hernandez, G. Yamanaka, S. Zhang, R. Rose, S. Weinheimer, R.J. Colonno, Efficacies of entecavir against lamivudine-resistant hepatitis B virus replication and recombinant polymerases in vitro, Antimicrob. Agents Chemother. 46 (2002) 2525–2532.

100. F. Li, R. Goila-Gaur, K. Salzwedel, N.R. Kilgore, M. Reddick, C. Mataallana, A. Castillo, D. Zoumplis, D.E. Martin, J.M. Orenstein, G.P. Allaway, E.O. Freed, C.T. Wild, PA-457: a potent HIV inhibitor that disrupts core condensation by targeting a late step in Gag processing, Proc. Natl. Acad. Sci. USA 100 (2003) 13555–13560.

101. C.-J. Liu, M.-Y. Lai, Y.-C. Chao, L.-Y. Liao, S.-S. Yang, T.-J. Hsiao, T.-Y. Hsieh, C.-L. Lin, J.-T. Hu, C.-L. Chen, P.-J. Chen, J.-H. Kao, D.-S. Chen, Interferon α-2b with and without ribavirin in the treatment of hepatitis B e antigen-positive chronic hepatitis B: a randomized study, Hepatology 43 (2006) 742–749.

102. S. Liu, H. Lu, A.R. Neurath, S. Jiang, Combination of candidate microbicides cellulose acetate 1,2-benzenedicarboxylate and UC781 has synergistic and complementary effects against human immunodeficiency virus type 1 infection, Antimicrob. Agents Chemother. 49 (2005) 1830–1836.

103. M. Liuzzi, P. Kibler, C. Bousquet, F. Harji, G. Bolger, M. Garneau, N. Lapuyre, R.S. McCollum, A.-M. Faucher, B. Simonneau, M.G. Cordingley, Isolation and characterization of herpes simplex virus type 1 resistant to aminothiazolylphenyl-based inhibitors of the viral helicase–primase, Antiviral Res. 64 (2004) 161–170.

104. N. Madani, A.L. Perdigoto, K. Srinivasan, Localized changes in the gp120 envelope glycoprotein confer resistance to human immunodeficiency virus entry inhibitors BMS-806 and #155, J. Virol. 78 (2004) 3742–3752.

105. W.C. Magee, K.Y. Hostetler, D.H. Evans, Mechanism of inhibition of vaccinia virus DNA polymerase by cidofovir diphosphate, Antimicrob. Agents Chemother. 49 (2005) 3153–3162.

106. P. Marcellin, T. Asselah, Resistance to adefovir α: a new challenge in the treatment of chronic hepatitis B, J. Hepatol. 43 (2005) 920–923.

107. P. Marcellin, T.T. Chang, S.G. Lim, M.J. Tong, W. Sievert, M.L. Shiffman, L. Jeffers, Z. Goodman, M.S. Wulfsohn, S. Xiong, J. Fry, C.L. Broussard, Adefovir diphosphoryl for the treatment of hepatitis B e antigen-positive chronic hepatitis B, N. Engl. J. Med. 348 (2003) 808–816.

108. S.J. Matthews, Entecavir for the treatment of chronic hepatitis B virus infection, Clin. Ther. 28 (2006) 184–203.

109. A.P. McCaffrey, H. Nakai, K. Pandey, Z. Huang, F.H. Salazar, H. Xu, S.F. Wieland, P.I. Marion, M.A. Kay, Inhibition of hepatitis B virus in mice by RNA interference, Nature Biotechnol. 21 (2003) 639–644.

110. C. McGuigan, H. Barucki, S. Blewett, A. Carangio, J.T. Erichsen, G. Andrei, R. Snoeck, E. De Clercq, J. Balzarini, Highly potent and selective inhibition of
varicella-zoster virus by bicyclic furo pyrimidine nucleosides bearing an aryl side chain, *J. Med. Chem.* 43 (2000) 4993–4997.

111. R. Mentel, U. Wegner, Evaluation of the efficacy of 2′,3′-dideoxycytidine against adenovirus infection in a mouse pneumonia model, *Antiviral Res.* 47 (2000) 79–87.

112. L. Naesens, P. Bonnafous, H. Agut, E. De Clercq, Antiviral activity of diverse classes of broad-acting agents and natural compounds in HHV-6-infected lymphoblasts, *J. Clin. Virol. (Suppl.)* (2006) S69–S75.

113. L. Naesens, L. Lenaerts, G. Andrei, R. Snoeck, D. Van Beers, A. Holý, J. Balzarini, E. De Clercq, Antiadenovirus activities of several classes of nucleoside and nucleotide analogues, *Antimicrob. Agents Chemother.* 49 (2005) 1010–1016.

114. V. Nair, G. Chi, R. Ptak, N. Neamati, HIV integrase inhibitors with nucleobase scaffolds: discovery of a highly potent anti-HIV agent, *J. Med. Chem.* 49 (2006) 445–447.

115. J. Neyts, P. Leyssen, E. Verbeke, E. De Clercq, Efficacy of cidofovir in a murine model for disseminated/progressive vaccinia, *Antimicrob. Agents Chemother.* 48 (2004) 2267–2273.

116. M. Nishikawa, K. Takashima, T. Nishi, R.A. Furuta, N. Kanzaki, Y. Yamamoto, J. Fujisawa, Analysis of binding sites for the new small-molecule CCR5 antagonist TAK-220 on human CCR5, *Antimicrob. Agents Chemother.* 49 (2005) 4708–4715.

117. T. Nitanda, X. Wang, H. Kumamoto, K. Haraguchi, H. Tanaka, Y.C. Cheng, M. Baba, Anti-human immunodeficiency virus type 1 activity and resistance profile of 2′,3′-didehydro-3′-deoxy-4′-ethynylthymidine in vitro, *Antimicrob. Agents Chemother.* 49 (2005) 3355–3360.

118. X.Y. Niu, Z.L. Peng, W.Q. Duan, P. Wang, H. Wang, Inhibition of HPV 16 E6 oncogene expression by RNA interference in vitro and in vivo, *Int. J. Gynecol. Cancer* 16 (2006) 743–751.

119. C.D. Novina, M.F. Murray, D.M. Dykxhoorn, P.J. Beresford, J. Riess, S.K. Lee, R.G. Collman, J. Lieberman, P. Shankar, P.A. Sharp, siRNA-directed inhibition of HIV-1 infection, *Nature Med.* 8 (2002) 681–686.

120. M.K. Osborn, A.S.F. Lok, Antiviral options for the treatment of chronic hepatitis B, *J. Antimicrob. Chemother.* 57 (2006) 1030–1034.

121. C. Osiowy, J.-P. Villeneuve, E.J. Heathcote, E. Giles, J. Borlang, Detection of rtN236T and rtA181V/T mutations associated with resistance to adefovir dipivoxil in samples from patients with chronic hepatitis B virus infection by the INNO-LiPA HBV DR Line Probe Assay (version 2), *J. Clin. Microbiol.* 44 (2006) 1994–1997.

122. G.R. Painter, K.Y. Hostetler, Design and development of oral drugs for the prophylaxis and treatment of smallpox infection, *Trends Biotechnol.* 22 (2004) 423–427.

123. D. Palliser, D. Chowdhury, Q.-Y. Wang, S.J. Lee, R.T. Bronson, D.M. Knipe, J. Lieberman, An siRNA-based microbicide protects mice from lethal herpes simplex virus 2 infection, *Nature* 439 (2006) 89–94.

124. J. Peng, Y. Zhao, J. Mai, W.K. Pang, X. Wei, P. Zhang, Y. Xu, Inhibition of hepatitis B virus replication by various RNAi constructs and their pharmacodynamic properties, *J. Gen. Virol.* 86 (2005) 3227–3234.

125. M.N. Prichard, K.A. Keith, D.C. Quenelle, E.R. Kern, Activity and mechanism of action of N-methanocarbathymidine against herpesvirus and orthopoxvirus infections, *Antimicrob. Agents Chemother.* 50 (2006) 1336–1341.

126. S.S. Printsevskaya, S.E. Solovieva, E.N. Olufuye, E.P. Mirchin, E.B. Isakova, E. De Clercq, J. Balzarini, M.N. Preobrazhenskaya, Structure-activity relationship studies of a series of antiviral and antibacterial aglycon derivatives of the glycopeptide antibiotics vancomycin, eremomycin, and dechloroeremomycin, *J. Med. Chem.* 48 (2005) 3885–3890.
127. X.F. Qin, D.S. An, I.S. Chen, D. Baltimore, Inhibiting HIV-1 infection in human T cells by lentiviral-mediated delivery of small interfering RNA against CCR5, Proc. Natl. Acad. Sci. USA 100 (2003) 183–188.

128. D.C. Quenelle, D.J. Collins, W.B. Wan, J.R. Beadle, K.Y. Hostetler, E.R. Kern, Oral treatment of cowpox and vaccinia virus infections in mice with ether lipid esters of cidofovir, Antimicrob. Agents Chemother. 48 (2004) 404–412.

129. D.C. Quenelle, K.A. Keith, E.R. Kern, In vitro and in vivo evaluation of isatin-β-thiosemicarbazone and marboran against vaccinia and cowpox virus infections, Antiviral Res. 71 (2006) 24–30.

130. P. Randhawa, N.A. Farasati, R. Shapiro, K.Y. Hostetler, Ether lipid ester derivatives of cidofovir inhibit polyomavirus BK replication in vitro, Antimicrob. Agents Chemother. 50 (2006) 1564–1566.

131. P.M. Reeves, B. Bommarius, S. Lebeis, S. McNulty, J. Christensen, A. Swimm, A. Chahroudi, R. Chavan, M.B. Feinberg, D. Veach, W. Bornmann, M. Sherman, D. Kalman, Disabling poxvirus pathogenesis by inhibition of Abl-family tyrosine kinases, Nature Med. 11 (2005) 731–739.

132. S.J. Robbins, R.J. Jackson, F. Fenner, S. Beaton, J. Medveczky, I.A. Ramshaw, A.J. Ramsay, The efficacy of cidofovir treatment of mice infected with ectromelia (mousepox) virus encoding interleukin-4, Antiviral Res. 66 (2005) 1–7.

133. K.R. Romines, G.A. Freeman, L.T. Schaller, J.R. Cowan, S.S. Gonzales, J.H. Tidwell, C.W. Andrews 3rd, D.K. Stammers, R.J. Hazen, R.G. Ferria, S.A. Short, J.H. Chan, L.R. Boone, Structure-activity relationship studies of novel benzophenones leading to the discovery of a potent, next generation HIV nonnucleoside reverse transcriptase inhibitor, J. Med. Chem. 49 (2006) 727–739.

134. P. Russ, P. Schelling, L. Scapozza, G. Folkers, E. De Clercq, V.E. Marquez, Synthesis and biological evaluation of 5-substituted derivatives of the potent antitherpes agent (North)-methanocarbathymine, J. Med. Chem. 46 (2003) 5045–5054.

135. M.S. Saag, Emtricitabine, a new antiretroviral agent with activity against HIV and hepatitis B virus, Clin. Infect. Dis. 42 (2006) 126–131.

136. M. Sato, T. Motomura, H. Aramaki, T. Matsuda, M. Yamashita, Y. Ito, H. Kawakami, Y. Matsuzaki, W. Watanabe, K. Yamataka, S. Ikeda, E. Kodama, M. Matsuoka, H. Shinkai, Novel HIV-1 integrase inhibitors derived from quinolone antibiotics, J. Med. Chem. 49 (2006) 1506–1508.

137. I.A. Scordi-Bello, A. Mosoian, C. He, Y. Chen, Y. Cheng, G.A. Jarvis, M.J. Keller, K. Hogarty, D.P. Waller, A.T. Prefo, B.C. Herold, M.E. Klotman, Candidate sulfonated and sulfated topical microbicides: comparison of anti-human immunodeficiency virus activities and mechanisms of action, Antimicrob. Agents Chemother. 49 (2005) 3607–3615.

138. P. Shankar, N. Manjunath, J. Lieberman, The prospect of silencing disease using RNA interference, JAMA 293 (2005) 1367–1373.

139. N. Sluis-Cremer, N. Hamamouch, A. San Félix, S. Velázquez, J. Balzarini, M.-J. Carmaras, Structure-activity relationships of [2′,5′-bis-O-(tert-butyldimethylsilyl)-beta-D-ribofuranosyl]-3′-spiro-5′-(4′-amino-1′,2′-oxathiole-2′,2′-dioxide)thymine derivatives as inhibitors of HIV-1 reverse transcriptase dimerization, J. Med. Chem. 49 (2006) 4834–4841.

140. D.F. Smeet, M.-H. Wong, K.W. Bailey, J.R. Beadle, K.Y. Hostetler, R.W. Sidwell, Effects of four antiviral substances on lethal vaccinia virus (IHD strain) respiratory infections in mice, Int. J. Antimicrob. Agents 23 (2004) 430–437.

141. R. Snoeck, Papillomavirus and treatment, Antiviral Res. 71 (2006) 181–191.

142. R. Snoeck, G. Andrei, B. Bodaghi, L. Lagneaux, D. Daelemans, E. De Clercq, J. Neyts, D. Schols, L. Naesens, S. Michelson, D. Bron, M.J. Otto, A. Bousseau,
C. Nemecek, C. Roy, 2-Chloro-3-pyridin-3-yl-5,6,7,8-tetrahydroindolizine-1-carboxamide (CMV423), a new lead compound for the treatment of human cytomegalovirus infections, *Antiviral Res.* 55 (2002) 413–424.

143. V. Soriano, M. Puoti, M. Bonacini, G. Brook, A. Cargnel, J. Rockstroh, C. Thio, Y. Benhamou, Care of patients with chronic hepatitis B and HIV co-infection: recommendations from an HIV-HBV international panel, *AIDS* 19 (2005) 221–240.

144. A. Spaltenstein, W.M. Kazmierski, J.F. Miller, V. Samano, Discovery of next generation inhibitors of HIV protease, *Curr. Topics Med. Chem.* 5 (2005) 1589–1607.

145. K.J. Stittelaar, J. Neyts, L. Naesens, G. van Amerongen, R.F. van Laviere, A. Holy, E. De Clercq, H.G.M. Nieters, E. Fries, C. Maas, P.G.H. Mulder, B.A.M. van der Zeijst, A.D.M.E. Osterhaus, Antiviral treatment is more effective than smallpox vaccination upon lethal monkeypox virus infection, *Nature* 439 (2006) 745–748.

146. J.M. Strizki, C. Tremblay, S. Xu, Discovery and characterization of vicriviroc (SCH 417690), a CCR5 antagonist with potent activity against human immunodeficiency virus type 1, *Antimicrob. Agents Chemother.* 49 (2005) 4911–4919.

147. K. Takashima, H. Miyake, N. Kanzaki, Y. Tagawa, X. Wang, Y. Sugihara, Y. Iizawa, M. Baba, Highly potent inhibition of human immunodeficiency virus type 1 replication by TAK-220, an orally bioavailable small-molecule CCR5 antagonist, *Antimicrob. Agents Chemother.* 49 (2005) 3474–3482.

148. S. Tang, M. Tan, J.P. McCoy Jr, Z.M. Zheng, Short-term induction and long-term suppression of HPV16 oncogene silencing by RNA interference in cervical cancer cells, *Oncogene* 25 (2006) 2094–2104.

149. C.L. Tremblay, F. Giguel, Y. Guan, T.-C. Chou, K. Takashima, M.S. Hirsch, TAK-220, a novel small-molecule CCR5 antagonist, has favorable anti-human immunodeficiency virus interactions with other antiretrovirals in vitro, *Antimicrob. Agents Chemother.* 49 (2005) 3483–3485.

150. F. van Bömmel, T. Wünsche, S. Mauss, P. Reinke, A. Bergk, D. Schurmann, B. Wiedenmann, T. Berg, Comparison of adefovir and tenofovir in the treatment of lamivudine-resistant hepatitis B virus infection, *Hepatology* 40 (2004) 1421–1425.

151. F. van Bömmel, B. Zöllner, C. Sarrazin, U. Spengler, D. Hüppe, B. Möller, H.-H. Feucht, B. Wiedenmann, T. Berg, Tenofovir for patients with lamivudine-resistant hepatitis B virus (HBV) infection and high HBV DNA level during adefovir therapy, *Hepatology* 44 (2006) 318–325.

152. K. Vermeire, K. Princen, S. Hatse, E. De Clercq, K. Dey, T.W. Bell, D. Schols, CADA, a novel CD4-targeted HIV inhibitor, is synergistic with various anti-HIV drugs in vitro, *Antimicrob. Agents Chemother.* 49 (2005) 3183–3185.

153. C. Watson, S. Jenkinson, W. Kazmierski, T. Kenakin, The CCR5 receptor-based mechanism of action of 873140, a potent allosteric noncompetitive HIV entry inhibitor, *Mol. Pharmacol.* 67 (2005) 1268–1282.

154. M. Westby, E. van der Ryst, CCR5 antagonists: host-targeted antivirals for the treatment of HIV infection, *Antiviral Chem. Chemother.* 16 (2005) 339–354.

155. P.W. White, A.-M. Faucher, M.-J. Massariol, E. Welchner, J. Rancourt, M. Cartier, J. Archambault, Biphenylsulfonacetic acid inhibitors of the human papillomavirus type 6 E1 helicase inhibit ATP hydrolysis by an allosteric mechanism involving tyrosine 486, *Antimicrob. Agents Chemother.* 49 (2005) 4834–4842.

156. T. Wu, M. Froeyen, V. Kempeneers, C. Pannecoque, J. Wang, R. Busson, E. De Clercq, P. Herdewijn, Deoxythreosyl phosphate nucleosides as selective anti-HIV agents, *J. Am. Chem. Soc.* 127 (2005) 5056–5065.

157. K. Wursthorn, M. Lutgehetmann, M. Dandri, T. Volz, P. Buggisch, B. Zöllner, T. Longerich, P. Schirmacher, F. Metzler, M. Zankel, C. Fischer, G. Currie, C. Brosgart,
J. Petersen, Peginterferon alpha-2b plus adefovir induce strong cccDNA decline and HbsAg reduction in patients with chronic hepatitis B, *Hepatology* **44** (2006) 675–684.

158. G. Yang, D.C. Pevear, M.H. Davies, M.S. Collett, T. Bailey, S. Rippen, L. Barone, C. Burns, G. Rhodes, S. Tohan, J.W. Huggins, R.O. Baker, R.L. Buller, E. Touchette, K. Waller, J. Schriewer, J. Neys, E. De Clercq, K. Jones, D. Hruby, R. Jordan, An orally bioavailable antipoxvirus compound (ST-246) inhibits extracellular virus formation and protects mice from lethal orthopoxvirus challenge, *J. Virol.* **79** (2005) 13139–13149.

159. H. Yang, S.-K. Kim, P.A. Kim, M. Reche, T.J. Morehead, I.K. Damon, R.M. Walsh, E.L. Reinherrz, Antiviral chemotherapy facilitates control of poxvirus infections through inhibition of cellular signal transduction, *J. Clin. Invest.* **115** (2005) 379–387.

160. P.J. Yates, R. Hazen, M. St. Clair, L. Boone, M. Tisdale, R.C. Elston, In vitro development of resistance to human immunodeficiency virus protease inhibitor GW640385, *Antimicrob. Agents Chemother.* **50** (2006) 1092–1095.

161. H. Yatsuji, C. Noguchi, N. Hiraga, N. Mori, M. Tsuge, M. Imamura, S. Takahashi, E. Iwao, Y. Fujimoto, H. Ochi, H. Abe, T. Maekawa, C. Taten, K. Yoshizato, F. Suzuki, H. Kumada, K. Chayama, Emergence of a novel lamivudine-resistant hepatitis B virus variant with a substitution outside the YMDD motif, *Antimicrob. Agents Chemother.* **50** (2006) 3867–3874.

162. H. Yeo, Y. Li, L. Fu, J.L. Zhu, E.A. Gullen, G.E. Dutschman, Y. Lee, R. Chung, E.S. Huang, D.J. Austin, Y.C. Cheng, Synthesis and antiviral activity of helioxanthin analogues, *J. Med. Chem.* **48** (2005) 534–546.

163. C. Ying, E. De Clercq, J. Neys, Selective inhibition of hepatitis B virus replication by RNA interference, *Biochem. Biophys. Res. Commun.* **309** (2003) 482–484.

164. D. Yu, Y. Sakurai, C.H. Chen, F.R. Chang, L. Huang, Y. Kashiwada, K.H. Lee, Anti-AIDS agents 69, Moronic acid and other triterpene derivatives as novel potent anti-HIV agents, *J. Med. Chem.* **49** (2006) 5462–5469.

165. M. Zeng, Y. Mao, G. Yao, H. Wang, J. Hou, Y. Wang, B.N. Ji, C.-N.P. Chang, K.F. Barker, A double-blind randomized trial of adefovir dipivoxil in Chinese subjects with HBeAg-positive chronic hepatitis B, *Hepatology* **44** (2006) 108–116.

166. S. Zhou, J.M. Breitenbach, K.Z. Borysko, J.C. Drach, E.R. Kern, E. Gullen, Y.C. Cheng, J. Zemlicka, Synthesis and antiviral activity of (Z)- and (E)-2,2-[bis(hydroxymethyl)cyclopropylidene]methylpurines and -pyrimidines: second-generation methyleneoxyclopropane analogues of nucleosides, *J. Med. Chem.* **47** (2004) 566–575.

167. S. Zhou, E.R. Kern, E. Gullen, Y.-C. Cheng, J.C. Drach, S. Tamiya, H. Mitsuya, J. Zemlicka, 9-(3-Fluoro-2-(hydroxymethyl)cyclopropylidene)methyl-adenines and -guanines. Synthesis and antiviral activity of all stereoisomers, *J. Med. Chem.* **49** (2006) 6120–6128.

168. X.-J. Zhou, B.A. Fieldman, D.M. Lloyd, G.C. Chao, N.A. Brown, Pharmacokinetics of telbivudine in healthy subjects and absence of drug interaction with lamivudine or adefovir dipivoxil, *Antimicrob. Agents Chemother.* **50** (2006) 2309–2315.

169. W. Zhu, A. Burnette, D. Dorjsuren, P.E. Roberts, M. Huleihel, R.H. Shoemaker, V.E. Marquez, R. Agbaria, S. Sei, Potent antiviral activity of north-methanoarabidymidine against Kaposi’s sarcoma-associated herpesvirus, *Antimicrob. Agents Chemother.* **49** (2005) 4965–4973.

170. F. Zoulim, Entecavir: a new treatment option for chronic hepatitis B, *J. Clin. Virol.* **36** (2006) 8–12.