1
Outlook of the Antiviral Drug Era, Now More Than 50 Years After
Description of the First Antiviral Drug

Erik De Clercq

1.1
Introduction: The Prehistory

More than 50 years ago, the synthesis of IDU (iododeoxyuridine), a thymidine
analogue, was described by Prusoff [1]. This compound would later become the first
antiviral drug to be licensed for (topical) use in the treatment of herpes simplex virus
(HSV) infections of the eye. In this sense, the advent of IDU marked the birth of the
antiviral drug era. There are now about 50 licensed antiviral compounds, half of them
are used for the treatment of AIDS, of which the viral origin was first recognized 27
years ago [2, 3] (2008 Nobel Prize for Medicine or Physiology was awarded to
Françoise Barré-Sinoussi and Luc Montagnier for their discovery of human immuno-
deficiency virus and to Harald zur Hausen for demonstrating the link between
human papilloma virus (HPV) and cervical cancer).

Was IDU truly the first antiviral? In retrospect, the antiviral chemotherapy era had
a rather slow and unremarkable start. The first compounds quoted to have antiviral
activity (against vaccinia virus) were the thiosemicarbazones [4, 5]. These compounds
were also found effective against vaccinia virus infection in mice and rabbits [6–8],
and one of the thiosemicarbazones, that is, N-methylisatin-β-thiosemicarbazone,
even entered clinical studies for the prophylaxis of smallpox [9] just when the
smallpox vaccination took over and made any further attempts to develop an
antipoxvirus drug apparently superfluous.

Then came the benzimidazole derivatives as inhibitors of influenza virus multi-
plication [10, 11], but despite the reported effectiveness of the 5,6-dichloro-1-β-D-
ribofuranosyl benzimidazole (DRB) [10, 11] against influenza virus multiplication, it
was not pursued further as a potential anti-influenza virus agent. Another benz-
imidazole derivative, 2-(1-hydroxybenzyl)benzimidazole (HBB), was found active
against the multiplication of poliovirus (and other enteroviruses) [12–14], but with
the successful implementation of the polio vaccine, just as we had witnessed for
smallpox, interest in developing an antiviral drug for poliovirus infections vanished.

IDU, soon to be followed by TFT (trifluorothymidine), could be considered as the
third, and successful, attempt to herald the antiviral chemotherapy era. IDU was first
considered as a potential antitumor agent [15] before it was shown by Herrmann to be active against HSV and vaccinia virus [16]. That IDU and TFT finally became antiviral drugs for the topical treatment of HSV eye infections, in particular HSV keratitis, is due to the pioneering work of Kaufman [17, 18].

1.2 Key Events in Antiviral Drug Development

Table 1.1 presents the key events in antiviral drug discovery, 1959 being the year when IDU was first described [1]. Ribavirin was the first low molecular weight compound described as a broad-spectrum antiviral agent (in 1972) by Sidwell et al. [19]. The combination of ribavirin with (pegylated) interferon-α has now become a standard treatment [20] for patients with chronic hepatitis C. That virus infections could be specifically tackled, without harm to the host cell, was heralded by the advent (in 1977) of acyclovir [21, 22], which is today still considered as the gold standard for the treatment of HSV infections. Two years after the discovery of HIV, in 1985, the first antiretrovirus agent (to become a drug 2 years later), AZT (zidovudine) was described [23], and this opened the search for, and development of, a wealth of new 2',3'-dideoxynucleoside analogues, now collectively referred to as nucleoside reverse transcriptase inhibitors (NRTIs).

In 1986, we described the first of a new class of broad-spectrum anti-DNA virus agents [24], namely, acyclic nucleoside phosphonates, several of which are active against the HIV and HBV reverse transcriptase and, therefore, referred to as nucleotide reverse transcriptase inhibitors (NtRTIs). Then followed in December 1989 and 1990 the description of a new concept for inhibiting the HIV-1 reverse transcriptase by nonnucleoside analogues (i.e., HEPT [25, 26] and TIBO [27]), giving rise to a still growing class of antiviral drugs, the nonnucleoside reverse transcriptase inhibitors (NNRTIs). With saquinavir, the year 1990 marked the birth of the rational design of HIV protease inhibitors (HIV PIs), which, in the mean time, has yielded 10 licensed drugs.

In 1992, we described an unusual class of compounds, the bicyclams as HIV inhibitors interacting with a viral uncoating event [28]. These compounds (prototype: AMD3100) would be, later on, shown to act as CXCR4 antagonists. Together with the CCR5 antagonists (the only licensed anti-HIV drug of this class of compounds being maraviroc), CXCR4 and CCR5 antagonists can be considered coreceptor inhibitors (CRIIs), targeted at the coreceptor usage of X4 and R5 HIV strains, respectively. The year 1993 marked the description of two totally different strategic options: (i) that of DP-178, which later on would become known as enfuvirtide as an HIV fusion inhibitor (FI) [29] and (ii) that of 4-guanidino-Neu5Ac2en, which later on would become known as zanamivir as a neuraminidase-based inhibitor (NAI) of influenza virus replication [30]. Then followed in 1998 the seminal observation that HSV replication could be inhibited at the DNA helicase–primase level by a 2-aminothiazole (T157602) [31] that would later give impetus to the development of helicase–primase inhibitors (HPIs) as potential anti-HSV drugs.
<table>
<thead>
<tr>
<th>Year</th>
<th>NRTIs</th>
<th>NtRTIs</th>
<th>HIV PIs</th>
<th>INIs</th>
<th>NAIs</th>
<th>HCV PIs</th>
<th>(Poxvirus inhibitors)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1959</td>
<td>IDU</td>
<td>Ribavirin</td>
<td>AZT</td>
<td>HEPT</td>
<td>Enfuvirtide</td>
<td>T157602</td>
<td>2′-C-methyl nucleosides</td>
</tr>
<tr>
<td>1966</td>
<td>Tenofovir</td>
<td>Adefovir</td>
<td>TDF</td>
<td>TIBO</td>
<td>Efavirenz</td>
<td>NRTIs</td>
<td>Valopicitabine</td>
</tr>
<tr>
<td>1986</td>
<td>cidofovir</td>
<td>HPMPA</td>
<td>(–)FTC</td>
<td>Emtricitabine</td>
<td>4′-Azidocytidine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1989</td>
<td>Nevirapine</td>
<td>Delavirdine</td>
<td>ABC</td>
<td>TMC120</td>
<td>Thiophene, 4′-Azidocytidine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1990</td>
<td>Indinavir</td>
<td>Lopinavir</td>
<td>Aplaviroc</td>
<td>Maraviroc</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1991</td>
<td>Ritonavir</td>
<td>Kivexa</td>
<td>Vicriviroc</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1992</td>
<td>Boceprevir</td>
<td>(–)FTC</td>
<td>AMD3100</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1993</td>
<td>Tipranavir</td>
<td>Indinavir</td>
<td>CCR5 antagonists</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1994</td>
<td>ATV</td>
<td>APL</td>
<td>Maraviroc</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1995</td>
<td>Nelfinavir</td>
<td>FTC</td>
<td>AMD3100</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1996</td>
<td>Amprenavir</td>
<td>BMS Channel</td>
<td>Maraviroc</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1997</td>
<td>Delavirdine</td>
<td>TMC120</td>
<td>Maraviroc</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1998</td>
<td>Amprenavir</td>
<td>Mosher's Channel</td>
<td>Maraviroc</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1999</td>
<td>Amprenavir</td>
<td>Mosher's Channel</td>
<td>Maraviroc</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td>Nelfinavir</td>
<td>Maraviroc</td>
<td>Maraviroc</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2001</td>
<td>Amprenavir</td>
<td>Maraviroc</td>
<td>Maraviroc</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2002</td>
<td>Amprenavir</td>
<td>Maraviroc</td>
<td>Maraviroc</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td>Amprenavir</td>
<td>Maraviroc</td>
<td>Maraviroc</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2004</td>
<td>Amprenavir</td>
<td>Maraviroc</td>
<td>Maraviroc</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td>Amprenavir</td>
<td>Maraviroc</td>
<td>Maraviroc</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NRTIs: nucleoside reverse transcriptase inhibitors
NtRTIs: nucleoside reverse transcriptase inhibitors
HIV PIs: HIV protease inhibitors
INIs: integrase inhibitors
NAIs: neuraminidase inhibitors
HCV PIs: HCV protease inhibitors
CRIs: coreceptor inhibitors
FIs: fusion inhibitors
HPIs: helicase–primase inhibitors
NRRIs: nucleoside RNA replicase inhibitors
NNRRIs: nonnucleoside RNA replicase inhibitors
Although considered an attractive target for two decades or so, the HIV integrase became a realistic target only when Hazuda et al. [32] demonstrated in 2000 it to be inhibited by the so-called diketo acids, which have yielded one integrase inhibitor (INI) that has already been formally approved (raltegravir) and another one under development (elvitegravir). Also described in 2000 was a pestivirus inhibitor (VP32947) [33] that hallmarked the search for inhibitors targeted at the RNA-dependent RNA polymerase (RdRp) of not only pestiviruses but also hepaciviruses (nonnucleoside RNA replicase inhibitors (NNRRI)). In 2003, Lamarre et al. published their pioneering observation that hepatitis C virus (HCV) replication could be inhibited by ciluprevir [34], which (although the compound itself was not further developed) generated the search for other HCV PIs. Also in 2003, Migliaccio et al. [35] reported that 2'-C-methyl-substituted ribonucleosides were inhibitory to the replication of HCV and other flaviviruses by acting as nonobligate chain terminators, thus inciting the search for nucleoside RNA replicase inhibitors (NRRIs).

While, since the days of methisazone, interest in developing antivirals for poxvirus infections (i.e., smallpox) died, the advent in 2005 of ST-246 testifies to the renewed interest in this area [36], and this is further demonstrated by the observations that poxvirus infections can be successfully suppressed through inhibitors of tyrosine kinases (Gleevec [37] and CI-1033 [38]).

1.3 Antiviral Drugs: Current State of the Art

Most of the antiviral agents that have been approved, and are used in the treatment of virus infections, are targeted at HIV, HBV, HCV, influenza virus, HSV, and other herpesviruses such as varicella zoster virus (VZV) and cytomegalovirus (CMV). More compounds for the treatment of HIV, HBV, HCV, HSV, VZV, CMV, and influenza virus and several other viral infections, for example, poxvirus (e.g., variola, vaccinia, and monkeypox), respiratory syncytial virus, hemorrhagic fever virus (e.g., Lassa, Rift Valley, Ebola, yellow fever, and dengue), and enterovirus (e.g., polio, Coxsackie, and Echo), either are in clinical or preclinical development or still have to be developed. The antiviral compounds that have been approved by the US FDA (Food and Drug Administration) are listed in Table 1.2.

1.4 Antiviral Drugs Active against Herpesviruses (i.e., HSV, VZV, and so on)

Starting from IDU and TFT, many more 5-substituted 2'-deoxyuridines were synthesized [39], the most prominent antiviral drug of this class of compounds being (E)-5-(2-bromovinyl)-2'-deoxyuridine (BVDU) [40]. Although selectively active against both HSV-1 and VZV, BVDU has been developed specifically for the treatment of VZV infections (i.e., herpes zoster) [41].
Table 1.2  Antiviral drugs approved by the US FDA.

<table>
<thead>
<tr>
<th>Registered brand name</th>
<th>Generic name</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anti-HIV compounds</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nucleoside reverse transcriptase inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retrovir</td>
<td>Zidovudine (AZT)</td>
<td>GlaxoSmithKline</td>
</tr>
<tr>
<td>Videx®, Videx® EC</td>
<td>Didanosine (ddi)</td>
<td>Bristol–Myers Squibb</td>
</tr>
<tr>
<td>Hivid®</td>
<td>Zalcitabine (ddC)</td>
<td>Roche</td>
</tr>
<tr>
<td>Zerit®</td>
<td>Stavudine (d4T)</td>
<td>Bristol–Myers Squibb</td>
</tr>
<tr>
<td>Epivir®, Zeffix®</td>
<td>Lamivudine (3TC)</td>
<td>GlaxoSmithKline</td>
</tr>
<tr>
<td>Ziagen®</td>
<td>Abacavir (ABC)</td>
<td>GlaxoSmithKline</td>
</tr>
<tr>
<td>Emtriva®</td>
<td>Emtricitabine ((—)FTC)</td>
<td>Gilead Sciences</td>
</tr>
<tr>
<td>Combivir®</td>
<td>Lamivudine + zidovudine</td>
<td>GlaxoSmithKline</td>
</tr>
<tr>
<td>Trizivir®</td>
<td>Abacavir + lamivudine + zidovudine</td>
<td>GlaxoSmithKline</td>
</tr>
<tr>
<td>Epzicom®</td>
<td>Abacavir + lamivudine</td>
<td>GlaxoSmithKline</td>
</tr>
<tr>
<td><strong>Nucleotide reverse transcriptase inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viread®</td>
<td>Tenofovir disoproxil fumarate</td>
<td>Gilead Sciences</td>
</tr>
<tr>
<td>Truvada®</td>
<td>Tenofovir disoproxil fumarate + emtricitabine</td>
<td>Gilead Sciences</td>
</tr>
<tr>
<td>Atripla®</td>
<td>Tenofovir disoproxil fumarate + efavirenz</td>
<td>Gilead Sciences and Bristol–Myers Squibb</td>
</tr>
<tr>
<td><strong>Nonnucleoside reverse transcriptase inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viramune®</td>
<td>Nevirapine</td>
<td>Boehringer Ingelheim</td>
</tr>
<tr>
<td>Rescriptor®</td>
<td>Delavirdine</td>
<td>Pfizer</td>
</tr>
<tr>
<td>Sustiva®, Stocrin®</td>
<td>Efavirenz</td>
<td>Bristol–Myers Squibb</td>
</tr>
<tr>
<td>Intelence®</td>
<td>Etravirine</td>
<td>Tibotec</td>
</tr>
<tr>
<td><strong>Protease inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fortovase®</td>
<td>Saquinavir</td>
<td>Roche</td>
</tr>
<tr>
<td>Norvir®</td>
<td>Ritonavir</td>
<td>Abbott</td>
</tr>
<tr>
<td>Crixivan®</td>
<td>Indinavir</td>
<td>Merck</td>
</tr>
<tr>
<td>Viracept®</td>
<td>Nelfinavir</td>
<td>Pfizer</td>
</tr>
<tr>
<td>Agenerase®, Prozet®</td>
<td>Amprenavir</td>
<td>GlaxoSmithKline</td>
</tr>
<tr>
<td>Kaletra®</td>
<td>Lopinavir + ritonavir</td>
<td>Abbott</td>
</tr>
<tr>
<td>Reyataz®</td>
<td>Atazanavir</td>
<td>Bristol–Myers Squibb</td>
</tr>
<tr>
<td>Lexiva®</td>
<td>Fosamprenavir</td>
<td>GlaxoSmithKline</td>
</tr>
<tr>
<td>Aptivus®</td>
<td>Tipranavir</td>
<td>Boehringer Ingelheim</td>
</tr>
<tr>
<td>Prezista®</td>
<td>Darunavir</td>
<td>Tibotec</td>
</tr>
<tr>
<td><strong>Viral entry inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coreceptor inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selzentry®, Celsentri®</td>
<td>Maraviroc</td>
<td>Pfizer</td>
</tr>
<tr>
<td>Fusion inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fuzeon®</td>
<td>Enfuvirtide (T-20)</td>
<td>Roche</td>
</tr>
</tbody>
</table>

(Continued)
### Table 1.2 (Continued)

<table>
<thead>
<tr>
<th>Registered brand name</th>
<th>Generic name</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Integrase inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isentress®</td>
<td>Raltegravir</td>
<td>Merck</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Anti-HBV compounds</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epivir®, Zeffix®</td>
<td>Lamivudine (3TC)</td>
<td>GlaxoSmithKline</td>
</tr>
<tr>
<td>Hepsera®</td>
<td>Adefovir dipivoxil</td>
<td>Gilead Sciences</td>
</tr>
<tr>
<td>Baraclude®</td>
<td>Entecavir</td>
<td>Bristol-Myers Squibb</td>
</tr>
<tr>
<td>Tizeka®, Sebivo®</td>
<td>Telbivudine</td>
<td>Idenix Pharmaceuticals</td>
</tr>
<tr>
<td>Viread®</td>
<td>Tenofovir disoproxil fumarate</td>
<td>Gilead Sciences</td>
</tr>
<tr>
<td>Intron A®</td>
<td>Interferon-α-2b</td>
<td>Schering-Plough</td>
</tr>
<tr>
<td>Pegasis®</td>
<td>Pegylated interferon-α-2a</td>
<td>Roche</td>
</tr>
<tr>
<td><strong>Antiherpesvirus compounds</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HSV and VZV inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zovirax®</td>
<td>Acyclovir (ACV)</td>
<td>GlaxoSmithKline</td>
</tr>
<tr>
<td>Zelitrex®, Valtrex®</td>
<td>Valaciclovir (VACV)</td>
<td>GlaxoSmithKline</td>
</tr>
<tr>
<td>Denavir®, Vectavir®</td>
<td>Penciclovir (PCV)</td>
<td>Novartis</td>
</tr>
<tr>
<td>Famvir®</td>
<td>Famciclovir (FCV)</td>
<td>Novartis</td>
</tr>
<tr>
<td>Herpid®, Stoxil®, Idoxene®, Virudox®</td>
<td>Idoxuridine (IDU, IUDR)</td>
<td>Yale University</td>
</tr>
<tr>
<td>Viroptic®</td>
<td>Trifluridine (TFT)</td>
<td>King Pharmaceuticals</td>
</tr>
<tr>
<td>Zostex®, Brivirac®, Zerpex®</td>
<td>Brivudin (BVDU)(^a)</td>
<td>Berlin Chemie/Menarini</td>
</tr>
<tr>
<td><strong>CMV inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cymevene®, Cytovene®</td>
<td>Ganciclovir (GCV)</td>
<td>Roche</td>
</tr>
<tr>
<td>Valcyte®</td>
<td>Valganciclovir (VGCV)</td>
<td>Roche</td>
</tr>
<tr>
<td>Foscavir®</td>
<td>Foscarnet</td>
<td>Astra Zeneca</td>
</tr>
<tr>
<td>Vistide®</td>
<td>Cidofovir (CDV)</td>
<td>Pfizer</td>
</tr>
<tr>
<td>Vitravene®</td>
<td>Fomivirsen</td>
<td>Novartis</td>
</tr>
<tr>
<td><strong>Anti-influenza virus compounds</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symmetrel®, Mantadix®, Amantin®</td>
<td>Amantadine</td>
<td>Endo Pharmaceuticals</td>
</tr>
<tr>
<td>Flumadine®</td>
<td>Rimantadine</td>
<td>Forest Laboratories</td>
</tr>
<tr>
<td>Relenza®</td>
<td>Zanamivir</td>
<td>GlaxoSmithKline</td>
</tr>
<tr>
<td>Tamiflu®</td>
<td>Oseltamivir</td>
<td>Roche</td>
</tr>
<tr>
<td>Virazole®, Virazid®, Viramid®</td>
<td>Ribavirin</td>
<td>Valeant Pharmaceuticals</td>
</tr>
<tr>
<td><strong>Anti-HCV compounds</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rebetol®</td>
<td>Ribavirin</td>
<td>Schering-Plough</td>
</tr>
<tr>
<td>Copegus®</td>
<td>Ribavirin</td>
<td>Roche</td>
</tr>
<tr>
<td>Pegasys®</td>
<td>Pegylated interferon-α-2a</td>
<td>Roche</td>
</tr>
<tr>
<td>Roferon A®</td>
<td>Interferon-α-2a</td>
<td>Roche</td>
</tr>
<tr>
<td>Intron A®</td>
<td>Interferon-α-2b</td>
<td>Schering-Plough</td>
</tr>
<tr>
<td>PEG-Intron®</td>
<td>Pegylated interferon-α-2b</td>
<td>Schering-Plough</td>
</tr>
<tr>
<td>Rebetron®</td>
<td>Interferon-α-2b + ribavirin</td>
<td>Schering-Plough</td>
</tr>
</tbody>
</table>

\(^a\) Not formally approved by the US FDA.
BVDU owes its antiviral selectivity to a specific phosphorylation by the HSV-1- and VZV-encoded thymidine kinase, just as acyclovir does, but compared to acyclovir, BVDU is a much more potent inhibitor of VZV replication. If BVDU is further converted to a bicyclic furano[2,3-d]pyrimidine nucleoside analogue (BCNA) carrying an aliphatic side chain interrupted by a phenyl moiety [42, 43], as in Cf 1743, the compound becomes exquisitely and exclusively active against VZV.

Although BVDU and acyclovir belong, respectively, to the pyrimidine and purine nucleoside analogues, they share, structurally, the same carboxamide pharmacophore (Figure 1.1), which may explain why they are both specifically recognized as substrate by the HSV- and VZV-encoded thymidine kinases. The same pharmacophore is found in other acyclic guanosine analogues such as ganciclovir and penciclovir and

![Figure 1.1 Pharmacophores in antiherpesvirus agents.](image-url)
penciclovir, again explaining the specificity of these compounds against HSV and VZV. Remarkably, the same pharmacophore is also found in ribavirin, which was described as a broad-spectrum antiviral agent, 5 years before acyclovir was reported (see Table 1.1), but in the case of ribavirin, the presence of the ribofuranosyl moiety primarily directs its antiviral activity spectrum toward RNA viruses due to an inhibitory action at the level of the IMP dehydrogenase [44–46].

While BVDU and acyclovir interact in their active triphosphate form with the viral DNA polymerase, the first phosphorylation step by the viral thymidine kinase required only to initiate the activation process, the HPIs seem to be directly targeted at the HSV helicase–primase UL5–UL8–UL52 complex [47]. The first HPI reported to inhibit HSV replication via interaction with the helicase component of this complex [31] was the 2-aminothiazole T-157602. The HPIs that were subsequently described and also found to be more effective than acyclovir and famciclovir against HSV infections in murine models of HSV-1 and HSV-2 infection [48–51], namely, BILS 179BS and BAY 57-1293, are also built upon the 2-aminothiazole scaffold (Figure 1.1). HPIs represent an exciting new avenue in the development of antivirals active against herpesviruses [47], but whether they represent an alternative (or additional) strategy to acyclovir (and acyclic guanosine analogues in general) will depend on their exact spectrum of antiviral activity, whether or not encompassing VZV (an issue that presently can only be speculated upon), and the readiness by which they elicit resistance mutations [52, 53] (an issue that needs continued vigilance).

1.5 Antiviral Drugs Active against Retroviruses (HIV)

The best known class of the antiretroviral agents is that of the nucleoside reverse transcriptase inhibitors, now containing seven members – zidovudine, didanosine,
zalcitabine, stavudine, lamivudine, abacavir, and emtricitabine – that are on the market [54]. What all these compounds have in common is that they are 2',3'-dideoxynucleoside analogues (Figure 1.2, NRTIs), which through the absence of a 3'-hydroxyl group inevitably act as chain terminators at the reverse transcriptase level.

The last three of the series, namely, lamivudine (3TC, originally described as its racemic form, BCH-189) [55], abacavir (1592 U89) [56], and emtricitabine ((–)

---

**NRTIs**

```
\ce{\text{HO}^{-}N_{3}^{-}CH_{3}} \rightarrow \ce{\text{HO}^{-}O_{2}^{-}CH_{3}} \rightarrow \ce{\text{HO}^{-}N_{2}^{-}CH_{3}}
```

\text{AZT (Zidovudine)} \quad \text{d4T (Stavudine)} \quad \text{R = H : 3TC (Lamivudine)}
\quad \text{R = F : (-)FTC (Emtricitabine)}

**NtRTIs**

```
\ce{\text{HO}-P\leftrightarrow O^{-}O^{-}CH_{3}} \rightarrow \ce{\text{HO}-P\leftrightarrow O^{-}O^{-}CH_{3}}
```

\text{PMEA (Adefovir)} \quad \text{(R)-PMPA (Tenofovir)}

**NNRTIs**

```
W229 \quad P95 \quad Y318 \quad H235 \quad P236 \quad K101 \quad Y188 \quad K103
```

\text{Butterfly-like shape} \quad \text{Etravirine} \quad \text{Rilpivirine (TMC278)}

---

*Figure 1.2*  Pharmacophores in antiretrovirus agents.
PIs

Saquinavir

Darunavir (TMC-114)

INIs

Raltegravir (MK-0518)

Elvitegravir (GS-9137)

CRIs (R5 strains)

Maraviroc

Vicriviroc (SCH-D)

Figure 1.2 (Continued)
FTC) [57, 58], correspond to the (−)- or l-enantiomeric form (whereas the first four have the natural d-form).

NtRTIs should be clearly distinguished from the NRTIs as they contain a phosphonate group \[ \begin{array}{c} \text{P} \\ \text{O} \\ \text{C} \end{array} \text{O} \] that is isosteric with the phosphate group \[ \begin{array}{c} \text{P} \\ \text{O} \\ \text{C} \end{array} \text{O} \] of the normal nucleotides.

To this class of compounds belong adefovir and tenofovir (Figure 1.2, NtRTIs) [59], used in their oral prodrug forms, adefovir dipivoxil and tenofovir disoproxil fumarate (TDF), in the treatment of hepatitis B virus (HBV) and HIV infections, respectively. TDF has since 2008 also been licensed for the treatment of HBV infections [60]. TDF is also commercially available, in combination with emtricitabine (Truvada®), and in combination with emtricitabine and efavirenz (Atripla®), for the treatment of HIV infections.

The HEPTand TIBO derivatives were the first nonnucleoside reverse transcriptase inhibitors to be described [61]. This class has now yielded an abundance of compounds, four of which have been formally approved (nevirapine, delavirdine, efavirenz, and etravirine) and a fifth is forthcoming (rilpivirine). All these compounds have a butterfly-like shape (Figure 1.2, NNRTIs), a term first coined by Ding et al. [62], and it has also been shown by crystallographic analysis [63].

All protease inhibitors (PIs) that have been licensed for clinical use (from saquinavir to darunavir, Figure 1.2, PIs) [54], with the exception of tipranavir, are built upon the hydroxyethylene scaffold \[ -\text{CH(OH)}-\text{CH}_2- \], which can be considered peptidomimetic and thus imitates the peptide linkage that has to be cleaved by the viral protease during the viral protein maturation process. PIs are generally used in combination with other antiretroviral classes. Given their common scaffold they may be expected to give similar potency, side effects, and resistance profiles.

Of the fusion inhibitors (FIs), the first and still the only FI used in the treatment of HIV-1 infections is enfuvirtide (structure as given in Ref. [64]), a 36-amino acid peptide, for which proof of concept in the clinic was provided by Kilby et al. [65] and the clinical efficacy further demonstrated by Lalezari et al. [66] and Lazzarin et al. [67]. Limitations to the widespread use of enfuvirtide are its parenteral administration (subcutaneous injection twice daily), the local induration it may cause, and the cost.

Of the coreceptor inhibitors, none is likely to be available soon for the treatment of X4 HIV infections (instead, the CXCR4 antagonist AMD3100 has been developed, and recently licensed, as a stem cell mobilizer for autologous transplantation in patients with hematological malignancies such as non-Hodgkin’s lymphoma or multiple myeloma [68]). Several CCR5 antagonists have been described for the treatment of R5 HIV infections [69]: only one (maraviroc) has been licensed for clinical use and a second one (vicriviroc) is forthcoming. It is difficult to discern what these compounds have in common structurally, except for the presence of a number of basic nitrogens (Figure 1.2, CRIs).
In HIV integrase inhibitors, the prime structural determinant is undoubtedly the diketo acid group, which was already evident in the first “diketo acid” derivative (L-731988) that was described [32] and which subsequently [70] led via L-870810 to raltegravir (MK0518) that has been licensed for clinical use after its clinical efficacy was clearly demonstrated [71, 72]. Next in line is elvitegravir (GS-9137), a quinolone 3-carboxylic acid derivative (which can also be considered a “diketo acid” derivative) (Figure 1.2, INIs). Being also a quinolone derivative, elvitegravir could theoretically act as a transcription inhibitor, but it has been ascertained that elvitegravir, just like L-870810, acts as a genuine INI [73]. Both raltegravir and elvitegravir are assumed to interfere with the strand transfer reaction of the HIV integrase, the mutations Q148K and T66I conferring the highest resistance to both drugs [74].

1.6 Antiviral Drugs Active against Hepatitis B Virus

There are at present seven drugs approved by the US FDA for the treatment of hepatitis B virus: interferon-α-2b (Intron A), lamivudine (3TC), adefovir dipivoxil, entecavir, peginterferon-α-2a (Pegasys), telbivudine, and tenofovir disoproxil fumarate (a few others, that is, clevudine (L-FMAU), emtricitabine ((−)FTC), valtorcitabine (valLdC), amdoxovir (DAPD), and racivir, are still under development). The anti-HBV agents have been reviewed recently [75]. Two of these compounds (lamivudine and tenofovir) are also used for the treatment of HIV infections, and as both HIV and HBV depend for their replication on a virus-associated reverse transcriptase (RT), it is not surprising that some of the RT inhibitors that are active against HIV are also active against HBV, and vice versa. However, there are exceptions; that is, entecavir and telbivudine (Figure 1.3) are specific inhibitors of HBV replication. They both are assumed to interact with the viral DNA polymerase, but how they do so has not been fully explained. Entecavir, if it is incorporated into the viral DNA, has to act as an obligatory chain terminator, but this is not necessarily so for telbivudine since the latter contains a 3′-hydroxyl group, theoretically allowing further chain elongation.

![Figure 1.3](image-url) Pharmacophores in anti-HBV agents.
1.7 Antiviral Drugs Active against DNA Viruses at Large

For the majority of DNA virus infections there is no specific (formalized) treatment, including polyoma-, papilloma-, and adenovirus, the herpesviruses Epstein–Barr virus (EBV) and human herpesvirus type 6 (HHV-6), and the whole family of poxviridae (including the orthopoxviruses variola, vaccinia, monkeypox, and cowpox), the parapoxviruses (i.e., orf), and mollusciviruses (i.e., molluscum contagiosum virus). Cidofovir, which has been formally licensed only for the treatment of CMV retinitis in AIDS patients, could be used “off label” for the treatment of other herpesvirus infections as well as polyoma-, papilloma-, adeno-, and poxvirus infections. The problem with cidofovir and all other acyclic nucleoside phosphonates, however, is that they have poor, if any, oral bioavailability, and to overcome this problem, alkoxyalkyl (i.e., hexadecyloxypropyl (HDP) and octadecyloxyethyl (ODE)) esters of cidofovir have been synthesized with high efficacy in the oral treatment of various (experimental) orthopoxvirus infections in mice [76, 77], as reviewed by Hostetler [78].

The parent compound of the acyclic nucleoside phosphonates is (S)-HPMPA (Figure 1.4) that was first described [24] in 1986. Then followed (S)-HPMPC [79] and, more recently, (R)-HPMPO-DAPy [80] and (S)-HPMP-5-azaC [81], and the HDP and ODE prodrugs of (S)-HPMP-5-azaC [82]. (R)-HPMPO-DAPy (Figure 1.4) proved more effective than postexposure smallpox vaccination in a lethal model of monkeypox virus infection in cynomolgus monkeys [83], and (S)-HPMP-5-azaC (Figure 1.4) proved to be a more potent and more selective antiviral agent than cidofovir (S)-HPMPC) [84]. The new acyclic nucleoside phosphonates (R)-HPMPO-DAPy and (S)-HPMP-5-azaC, and alkoxyalkyl esters thereof, offer a wealth of potential applications in the broad field of DNA (pox, adeno, polyoma, papilloma, and herpes) virus infections, which have so far remained largely untapped.

\[
\begin{align*}
 R = H : (S)-HPMPA \\
 R = \text{NH}_2 : (S)-HPMP-DAP \\
 X = \text{CH} : (S)-HPMPC \\
 X = \text{N} : (S)-HPMP-5-azaC \\
\end{align*}
\]

Figure 1.4 Pharmacophores in broad-spectrum anti-DNA virus agents.
1.8 Antiviral Drugs for Influenza A Virus Infections

Ever since amantadine was discovered as an inhibitor of influenza A virus replication [85], it has been considered a potential strategy for the therapy and prophylaxis of influenza A virus infections [60], but amantadine has also become notorious for rapidly leading to resistance development, probably a consequence of the specificity of its interaction with the M2 protein of influenza A virus. Various other strategies have been considered in the war against influenza [86], among which are ribavirin, viramidine, siRNAs, and phosphorothioate oligonucleotides, interferon (inducers), and viral RdRp inhibitors [87]. The most fascinating [88, 89] of the RdRp inhibitors is undoubtedly T-705.

At present, the neuraminidase inhibitors are still considered the most likely candidates to be used not only to curtail the annual recurrences of seasonal influenza (A (H1N1), A (H3N2), and influenza B) but also to prevent pandemics with any influenza A virus infection, whether avian (i.e., influenza A H5N1) or any new influenza A (H1N1) strain, such as the recent “Mexican” variant.

Neuraminidase inhibitors do have a very specific interaction with the viral neuraminidases (sialidase) [86] (Figure 1.5), “trapping” the newly formed virions

![Chemical structures of neuraminidase inhibitors](image)

Figure 1.5 Pharmacophores in neuraminidase (sialidase) inhibitors.
at the cell surface, thus preventing the release of these progeny influenza virions from the cells (in which they have been formed) [87]. Unfortunately, influenza A seems to readily develop resistance against neuraminidase inhibitors such as oseltamivir (Tamiflu®) [89]. On the one hand, this points to the specificity of oseltamivir as an antiviral agent and, on the other hand, it argues for a close surveillance of the possible emergence of resistance with the extended use of neuraminidase inhibitors such as oseltamivir.

1.9 Antiviral Drugs for Hepatitis C Virus

Standard care for hepatitis C nowadays consists of the administration of pegylated interferon-α-2a, in combination with ribavirin. Yet, specific anti-HCV agents are under development that are targeted at either the HCV (serine) protease or HCV RdRp. The most advanced among the HCV protease inhibitors are telaprevir [90] and boceprevir [91, 92]. The efficacy of telaprevir, in combination with pegylated interferon and ribavirin, in the treatment of hepatitis C has recently been demonstrated [93, 94]. The first HCV PI to be described and to show antiviral activity in humans was ciluprevir (BILN 2061) [34]. While ciluprevir and a successor thereof, TMC-435350 [95], do have a macrocyclic structure (not shown), telaprevir and boceprevir are built upon a (poly)peptide scaffold.

Like the HIV RT, the HCV RdRp can be targeted at both the catalytic site (by NRRIs) and the allosteric site (by NNRRIs). A characteristic of the anti-HCV activity of NRRIs is the presence of the 2′-C-methyl pharmacophore, as in 2′-C-methyladenosine, 2′-C-methylguanosine, 2′-C-methylcytidine, 7-deaza-2′-C-methyladenosine, and 2′-deoxy-2′-fluoro-2′-C-methylcytidine (Figure 1.6, NRRIs). 2′-Methyl-substituted ribonucleosides are active not only against hepaciviruses such as HCV but also against pestiviruses, such as bovine viral diarrhea virus (BVDV), and flaviviruses, such as yellow fever and West Nile [35]. They act as nonobligate chain terminators of the RdRp [35]. The first NRRI to enter the clinic was valopicitabine (NM 283: 3′-valine ester of 2′-C-methylcytidine). It was also the first to be discontinued for further development. An exception to the rule that the nucleoside analogues active against HCV should contain a 2′-C-methyl group is the 4′-azidocytidine (R1479) [96], and like valopicitabine, this compound has apparently not been further developed.

Resulting from the first wave of NNRRIs were thiophene, 2-carboxylic acid, benzimidazole, and benzothiadiazine derivatives [97], further extended by various other derivatives among which was the benzofuran derivative HCV-796 [98]. The latter proved, in fact, highly active against the HCV replicon system [99], but its further development has apparently been stopped. One of the most potent anti-HCV agents (in development) acting as an NNRI is GS-327073 (Figure 1.6, NNRRIs). It has an EC50 of 0.002–0.004 μM in the HCV (genotype 1b) replicon system. GS-327073 is based upon the 5-[(4-bromophenyl)methyl]-2-phenyl-5H-imidazo[4,5-c]pyridine BPIP skeleton, which was first identified as a potent
and selective inhibitor of the replication of pestiviruses such as BVDV [100]. BPIP was from the start recognized as an inhibitor of RdRp, the “finger” domain of the enzyme being its target. Further chemical modifications of the BPIP skeleton led to the identification of GS-327073 as a potent and selective NNRRI of the HCV RdRp, again with the “finger” domain being the target site [101].

Figure 1.6 Pharmacophores in anti-HCV agents.
1.10 Antiviral Drugs for Poxviruses (i.e., Variola, Vaccinia, and so on)

Poxviruses (such as variola, vaccinia, cowpox, and monkeypox) are the largest of all viruses and contain the largest set of genes encoding for specific viral proteins that could be considered targets for chemotherapeutic intervention. At present, cidofovir (\(\text{S-HPMPC}\)) has remained the only drug that could be used, albeit off label, both for the therapy and short-term prophylaxis of smallpox (should it, for example, occur in the context of a bioterrorist attack) and monkeypox and for the treatment of the complications of vaccinia that could arise in immunosuppressed patients inadvertently inoculated with the smallpox vaccine [60, 102]. If needed, cidofovir could be used in its oral prodrug form (i.e., hexadecylpropyl (HDP)-cidofovir), now known as CMX001. In the mean time, a new compound ST-246 (Figure 1.7) has come along, developed by SIGA Technologies Inc., which appears to inhibit variola virus and other orthopoxvirus infections by inhibiting the F13L phospholipase involved in extracellular virus production [36, 60, 103]. ST-246 acts synergistically with CMX001 [104], which throws open interesting prospects for this drug combination in the treatment of orthopoxvirus infections. Most important would be to know whether ST-246 is efficacious against smallpox, or the complications of smallpox vaccination such as eczema vaccinatum. A recent case of severe eczema vaccinatum in a household contact of a smallpox vaccinee illustrates the importance of the complications of smallpox vaccination and the possible impact ST-246 may have in such case(s) [60, 105].

In addition to specifically viral protein-targeted agents (such as ST-246), a number of compounds that interfere with cellular signal transduction, by inhibiting protein tyrosine kinases, such as STI-571 (Gleevec) [37] and 4-anilinoquinazoline CI-1033 [38], have been reported to strongly inhibit poxvirus (i.e., vaccinia virus) infections \textit{in vivo}. These observations point to the options still available to treat poxvirus infections \textit{in vivo}. 

![Figure 1.6 (Continued)](image-url)
Figure 1.7 Inhibitors of poxvirus replication.
1.11

Further Options to Treat Virus Infections

Other, still, investigational strategies for the treatment of HIV and HCV infections have been described recently [98]. The farthest developed in the clinic (phase II) is a nonimmunosuppressive derivative of cyclosporin A, Debio-025 (structure as shown in Ref. [106]), a cyclophilin binding agent that has potent activity against both HCV [107] and HIV-1 [108]. Debio-025 has shown potent anti-HCV activity in patients coinfected with HCV and HIV-1 [109].

For the treatment of poliovirus, and other enterovirus, and rhinovirus infections, a large variety of antipicornavirus agents have been described [106], the last in the series being a protein 3A inhibitor, TTP-8307 [110]. None of these compounds, however, has been developed from a clinical viewpoint. Likewise, increasingly significant attempts have been undertaken to find specific inhibitors for flavivirus (such as dengue virus) and other hemorrhagic fever virus infections [89], and for these virus infections, a “druggable” candidate compound is still eagerly awaited.

While the search for new therapeutic options to treat influenza virus infections has been continuously spurred by the emergence of new virus strains with pandemic “allures,” relatively little effort has been made to find or develop new therapeutics for respiratory syncytial virus (RSV) infections. Of significant potential in this regard might be a benzodiazepine, RSV604 (structure as shown in Ref. [111]), which seems to be targeted at the RSV nucleocapsid protein and has proceeded to phase II clinical trials [111].

1.12

Conclusions

In addition to the some 50 antivirals that have been formally approved, now exactly 50 years after the first antiviral drug (IDU) was synthesized, the number of potential antiviral drug candidates is steadily growing [112]. Most of the antiviral drug development efforts have been focused on HIV, followed by HCV and HBV, and influenza virus coming next because of its capriolic incidence. Also, hemorrhagic fever virus (and related encephalitis) infections, because of their global impact, should and have received accrued attention from a therapeutic viewpoint.

Other virus infections, such as herpes simplex and polio, have received relatively little attention because it has been felt they are sufficiently contained by established procedures, acyclovir therapy and vaccination, respectively. The methodology to design new antiviral drug strategies has gradually shifted from “serendipitous” screening to “rational” structure-based drug design, although in most instances this rational approach boiled down to the sheer chemical modification of a known scaffold or building on further from a known pharmacophore.

Surprisingly, the combination drug strategy that has been diligently worked out for HIV, primarily to prevent HIV drug resistance development, has not (yet) been exploited or even explored for other viruses such as HBV, HSV, or influenza. For
HCV, as for HIV, it is believed that it will be necessary to combine different drugs acting by different mechanisms, but before this could be done, the individual drugs have to be identified and approved.

Most of the antiviral drugs now in, or considered for, clinical use are targeted at specific viral events, enzymes (i.e., polymerases, proteases), or processes (i.e., virus–cell fusion). The observation that protein kinase inhibitors such as Gleevec and anilinoquinazolines have antiviral activities (e.g., against poxviruses) should signal a broader applicability of these protein kinase inhibitors. Potential usefulness in the treatment of virus infections may also extend to various other protein kinase inhibitors (such as flavopiridol and rapamycin) [113].

Acknowledgment

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

References


10 Tamm, I., Folkers, K., Shunk, C.H., and Horsfall, F.L., Jr. (1954) Inhibition of influenza virus multiplication by N-


De Clercq, E. (1980) Antiviral and antitumor activities of 5-substituted 2'-


