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Twenty-Six Years of Anti-HIV Drug Discovery: Where Do We Stand and Where Do We Go?

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Introduction

The human immunodeficiency virus (HIV[a]) has now been established as the causative agent of the acquired immunodeficiency syndrome (AIDS) for over 20 years.[1,2] During this time an unprecedented success has been achieved in discovering anti-HIV drugs as reflected by the fact that there are now more drugs approved for the treatment of HIV than for all other viral infections taken together. The currently Food and Drug Administration (FDA) approved anti-HIV drugs can be divided into seven groups: nucleoside reverse transcriptase inhibitors (NRTIs), nucleotide reverse transcriptase inhibitors (NtRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion inhibitors (FIs), co-receptor inhibitors (CRIs), and integrase inhibitors (INIs). This arsenal of drugs, which is used in combinations, has moved the prognosis of HIV patients from that of high morbidity and mortality to, for many at least, a chronic, manageable but still complex disease.[3−5] However, the use of these drugs has been relatively limited by their toxicity,[6] drug resistance development,[7] and more worryingly, the fact that some newly HIV-infected patients carry viruses that are already resistant to the currently approved AIDS treatments.[8] These issues along with drug-related side effects as well as, in some cases, poor tolerability of these drugs make it apparent that new anti-HIV drugs with acceptable toxicity and resistance profiles and, more importantly, new anti-HIV agents with novel mechanisms of action are clearly needed.

HIV Life Cycle and Anti-HIV Drug Design

The HIV life cycle encompasses several crucial steps, starting from the attachment of the virus to the host cell membrane and finishing with the release of progeny virions from the cell, as summarized in Figure 1. The HIV life cycle commences by a specific interaction between the virion glycoprotein gp120 on the outer membrane and the CD4 receptor on the host cell surface. This reaction results in a conformational change allowing the interaction of gp120 with the chemokine co-receptor CXCR4 or CCR5. This is then followed by further conformational changes that expose a fusogenic peptide, which anchors into the host cell membrane. Once the viral envelope and cell membrane have fused, the virion is decapsidated releasing the viral RNA into the host cell's cytoplasm. Through the reverse transcription, the viral RNA is transcribed to viral double-stranded DNA. This process is catalyzed by an RNA-dependent DNA polymerase, also known as reverse transcriptase, which is encoded by the viral genome. The viral DNA is then integrated into the host chromosome, and after transcription (facilitated by regulatory proteins Tat and Rev, which are themselves viral gene products) and translation into viral proteins using the cells' machinery, the assembly of the Gag and Gag-Pol polyproteins occurs near the cell membrane.[9,10] During viral assembly, two copies of single-stranded viral RNA are incorporated into the virion, which then buds off from the cell, taking with it part of the host cell membrane. Soon after budding, viral protease cleaves the Gag-Pol polyprotein to generate a mature, functional virion.[10]

Generally, antiviral drugs could, in principle, be targeted at either viral proteins or cellular proteins. The first approach is likely to yield more specific, less toxic compounds, with a narrow spectrum of activity and a higher likelihood of virus drug resistance development. The second approach, however, might afford anti-HIV drugs with a broader activity spectrum and less chance of resistance but higher likelihood of toxicity.[9] In anti-HIV drug discovery, Mitsuya and Broder were among the first to propose possible strategies for antiviral therapy of AIDS (Table 1).[11] With these suggestions (Table 1), extensive research has been conducted into discovering anti-HIV drugs, and nowadays (2009) there are 25 approved anti-HIV drugs that belong to 7 different classes of drugs as discussed below.

Current Treatments and Future Prospects

Nucleoside Reverse Transcriptase Inhibitors (NRTIs). The first anti-HIV drug that was ever approved for the treatment of AIDS was the nucleoside reverse transcriptase inhibitor 3′-azido-2′,3′-dideoxythymidine[12] (**1**), which is a nucleoside analogue that produces its activity by inhibiting the functioning of the HIV reverse transcriptase. Since then, there has been extensive research into identifying nucleoside-based compounds with good inhibitory activities of HIV reverse transcriptase. As a result, several nucleoside analogues, mainly 2′,3′-dideoxynucleosides, have been identified and

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[a] Abbreviations: AIDS, acquired immunodeficiency syndrome; CBAs, carbohydrate-binding agents; CCD, catalytic core domain; CRIs, co-receptor inhibitors; CTD, carboxylic-terminal domain; EIs, entry inhibitors; FDA, Food and Drug Administration; FIs, fusion inhibitors; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; INIs, integrase inhibitors; LDL, low density lipoprotein; NRTIs, nucleoside reverse transcriptase inhibitors; NNRTIs, nonnucleoside reverse transcriptase inhibitors; NTD, amino-terminal domain; NtRTIs, nucleotide reverse transcriptase inhibitors; PIs, protease inhibitors; RNase H, ribonuclease H; SHIV, simian human immunodeficiency virus.

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approved for treating HIV patients. Indeed, as well as compound **1**, there are currently six more NRTIs approved for use in the clinics: 2′,3′-didehydro-2′,3′-dideoxythymidine[13] (**2**), 2′,3′-dideoxycytidine[13] (**3**), 2′,3′-dideoxyinosine[14] (**4**), (1*S*,4*R*)-4-[2-amino-6-(cyclopropylamino)-9*H*-purin-9-yl]-2-cyclopentene-1-methanol[15] (**5**), (−)-2′,3′-dideoxy-5-fluoro-3′-thiacytidine[16] (**6**), and (−)-2′,3′-dideoxy-3′-thiacytidine[17] (**7**) (Figure 2). These agents are generally designed via three different ways: (1) modifications in the sugar moiety, e.g., **2**, (2) modifications in the nucleic base moiety, e.g., **4**, and (3) modifications in both the sugar and base moieties, e.g., **5** (Figure 2).

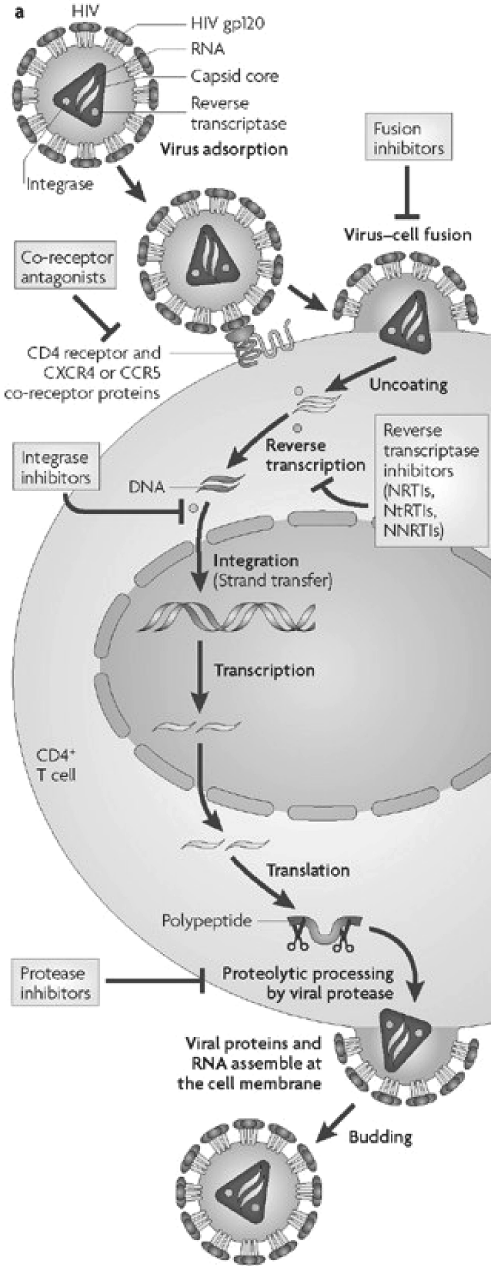

Figure 1. HIV lifecycle. Reprinted by permission from Macmillan Publishers Ltd.: *Nature Reviews Drug Discovery* (http://www.nature.com/nrd/index.html) (De Clercq, E. Strategies in the design of antiviral drugs. *Nat. Rev. Drug Discovery* 2002, *1*, 13−25),[9] Copyright 2002.

NRTIs produce their anti-HIV effects by inhibiting the activity of the HIV reverse transcriptase.[18] In order for these agents to produce such effects, they have to be phosphorylated consecutively by cellular kinases to their triphosphate derivatives.[18,19] As all NRTIs follow the same mechanism of inhibition of HIV reverse transcriptase, only the mechanism of action of **3** is included here as a representative for this class of drugs (Figure 3).[9] Compound **3** is phosphorylated by deoxycytidine kinase, deoxycytidine monophosphate kinase, and nucleoside diphosphate kinase to form the monophosphate, diphosphate, and the active triphosphate derivative of **3**, respectively. This active moiety is then incorporated into the growing DNA by cellular DNA polymerases. The incorporation of **3** into the growing DNA results in terminating the elongation of the growing DNA double strand. This is mainly due to the fact that compound **3** and generally all NRTIs lack the 3′-hydroxyl group; therefore, they prevent the incorporation of the incoming nucleotide. One of the mechanisms by which resistance to chain-terminating NRTIs might arise is through removal of the chain-terminating residue, a kind of repair reaction involving pyrophosphorolysis, which can be regarded as the opposite of the reverse transcriptase reaction.[9]

It is worth noting that the three consecutive intracellular phosphorylation reactions required for the activation of NRTIs represent a problematic step for many nucleoside analogues. In particular, the first phosphorylation step, which results in the formation of the nucleoside analogue monophosphate, is considered to be the most difficult. To overcome this problem, a series of prodrug strategies aimed at the delivery of nucleoside analogues monophosphates have been developed.[20] Examples of such prodrug strategies include phosphoramidates[21] and cyclosaligenyl (*cyclo*Sal),[22] which both have been shown to improve the anti-HIV activities of numerous anti-HIV nucleoside-based drugs. The application of either the phosphoramidates "ProTide" approach and the *cyclo*Sal strategy was successful in delivering the monophosphate derivative of **2** into cells, which was subsequently further phosphorylated to the active triphosphate form.[23,24] Thus, there was a significant increase in anti-HIV activity compared to that seen with the parent nucleoside under the same testing conditions. Another

Table 1. Summary of the Possible HIV Targets and Interventions[a]

stage of HIV lifecycle	potential intervention
Binding to target cell	Antibodies to the virus or cell receptor
Early entry to target cell	Drugs that block fusion or interfere with retroviral uncoating
Transcription of RNA to DNA by reverse transcriptase	Reverse transcriptase inhibitors
Degradation of viral RNA in the RNA−DNA hybrid	Inhibitors of RNase H activity
Integration of DNA into the host genome	Drugs that inhibit "integrase" function
Expression of viral genes	"Antisense" constructs; inhibitors of the tat protein or art/trs protein
Viral component production and assembly	Myristoylation, glycosylation, and protease inhibitors
Budding of virus	Interferons

[a] Adapted by permission from Macmillan Publishers Ltd: *Nature* (http://www.nature.com/nature/index.html) (Mitsuya, H.; Broder, S. Strategies for antiviral therapy of AIDS. *Nature* **1987**, *325*, 773−778),[11] Copyright 1987.

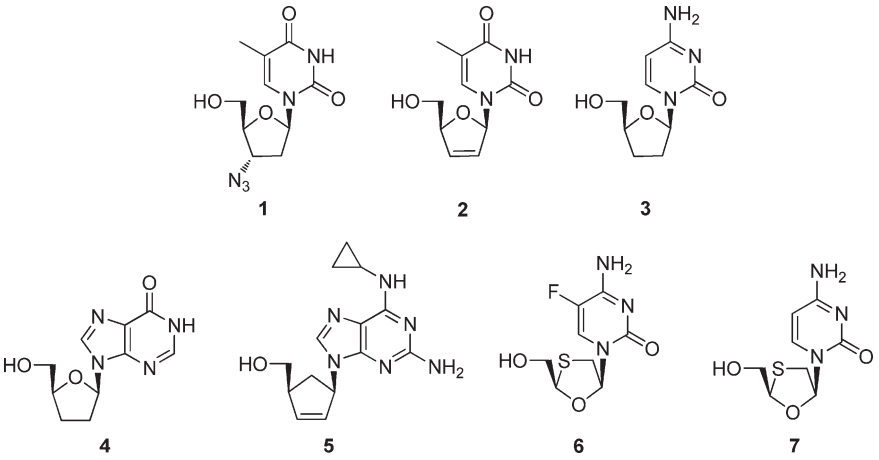

Figure 2. Structures of the currently FDA-approved anti-HIV NRTIs.

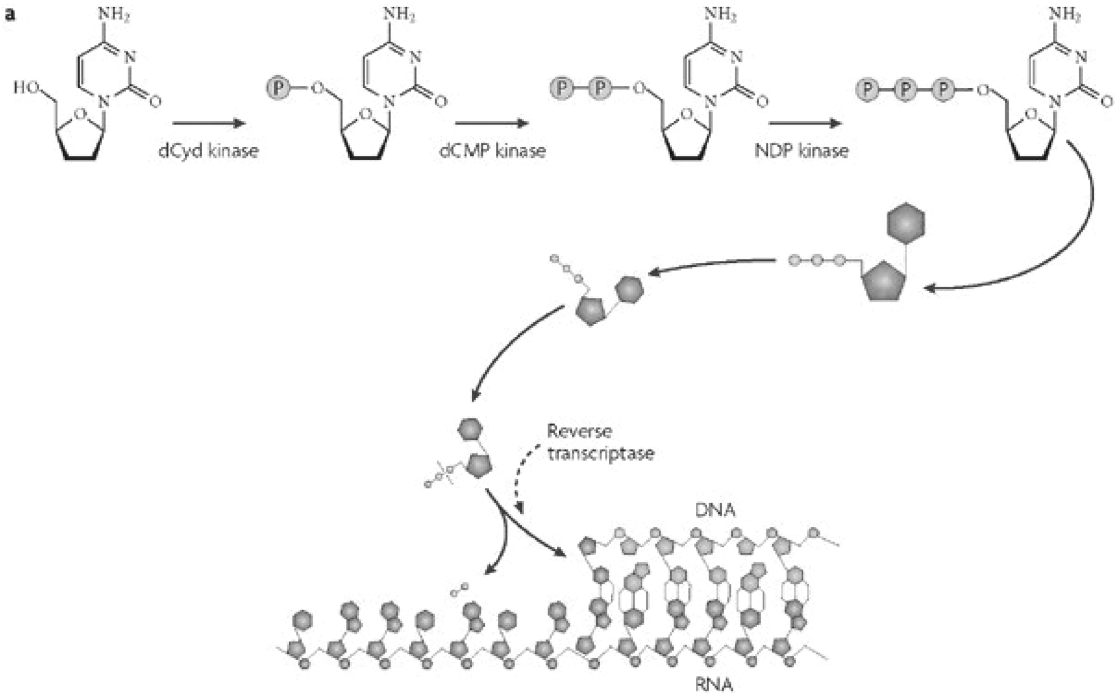

Figure 3. Mechanism of action of the NRTI 3 as a representative for the mechanism of action of NRTIs. Reprinted by permission from Macmillan Publishers Ltd.: *Nature Reviews Drug Discovery* (http://www.nature.com/nrd/index.html) (De Clercq, E. Strategies in the design of antiviral drugs. *Nat. Rev. Drug Discovery* 2002, *1*, 13−25),[9] Copyright 2002.

example of the success of these monophosphate prodrug strategies is the report by McGuigan et al.[25] on the application of the phosphoramidate approach to the carbocyclic derivative of (−)-2′,3′-didehydro-2′,3′-dideoxyadenosine (structure not disclosed), which resulted in a 9000-fold improvement in in vitro activity versus HIV. Nevertheless, to date there has been no "ProTide" approved for clinical use.

In addition to the presently approved seven NRTIs (Figure 2), there are currently four more undergoing either phase II or phase III clinical trials (Figure 4): apricitabine[26] (**8**), racivir[27] (**9**), amdoxovir[28] (**10**), and elvucitabine[29] (**11**). Of these agents, compound **8**, which is a deoxycytidine analogue, is the one that has so far progressed furthest in clinical development. It shows potent anti-HIV activity both in vitro[30,31] and in vivo,[32,33] and it retains its activity against virus strains resistant to the currently approved NRTIs.[30,31] Recent clinical studies highlighted the absence of resistance and serious side effects as well as sustainability of activity for a period of over 2 years.[34] With **8** having been granted fast track approval status by the FDA, it might (very soon) well be the eighth NRTI to be approved for clinical use as an anti-HIV treatment.

Compound **9**, which is a 50:50 mixture of the β-enantiomers of **6**, has been shown to possess potent anti-HIV activity both in vitro[35] and in vivo.[36−38] It has also shown good bioavailability, and its pharmacokinetic profile supports once-daily dosing.[38] Phase I/II data indicated that once-daily dosing of **9** in combination with **2** and efavirenz[39] (**15**) resulted in potent anti-HIV activity in antiretroviral naive HIV-infected patients.[40] Recently, in vivo data showed **9** to possess good safety and efficacy in patients with virus strains carrying the M184V mutation.[41]

Compound **10**, a guanosine analogue (diaminopurine dioxolane), gets deaminated inside the cell by adenosine deaminase, resulting in the formation of dioxolane guanine

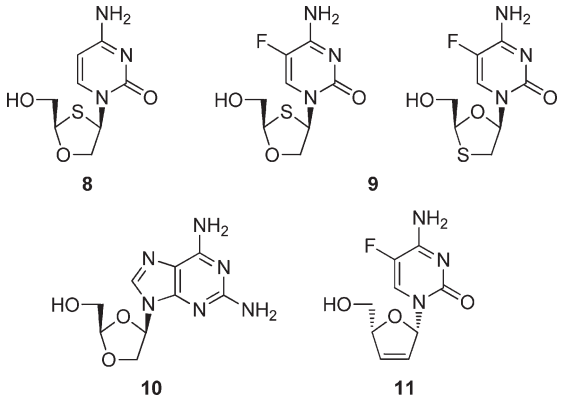

Figure 4. NRTIs currently undergoing either phase II or phase III of clinical trials.

(structure not disclosed), which is in turn phosphorylated to the triphosphate. Interestingly, the triphosphate of the deaminated product shows greater potency than the diaminopurine dioxolane. Compound **10** shows good activity in vitro against both wild type and some strains of the virus that are resistant to **1** and **7**,[42−44] as well as against multi-NRTIs resistant strains with the codon 69 insertion.[45] Although phase I/II studies showed significant reduction in HIV-1 RNA levels in HIV-infected subjects, 5 out of the 18 subjects used in this study demonstrated lens opacities during the study.[46] Compound **10** also showed good activity in vivo when used alone or in combination with **1**.[46,47] It is worth noting that in phase I/II studies, some subjects demonstrated lens opacities.[46] A number of efforts have been reported in the literature on the design of various prodrugs of **10** and its deaminated derivative in order to improve their solubility and pharmacological profiles.[48]

Another NRTI currently undergoing clinical trials is compound **11**, which is an L-deoxycytidine analogue with a fluorine atom on position 5. It has demonstrated potent in vitro activity against wild-type and against HIV resistant to several other nucleoside analogues.[49−51] In late 2008, data from a 48-week phase II study indicated that **11** showed safety and efficacy profiles similar to **7** in HIV-infected patients.[52] Notably, no serious side effects were reported in this study even though in earlier studies bone marrow suppression in some patients was noted.[53] This was thought to be due to the high doses of **11** employed in that particular study (50 and 100 mg per day).

Nucleotide Reverse Transcriptase Inhibitors (NtRTIs). In contrast to nucleoside reverse transcriptase inhibitors, nucleotide reverse transcriptase inhibitors are already equipped with a phosphonate group that cannot be cleaved by hydrolyzes (esterases), making these compounds not easily cleaved off once incorporated at the 3′-terminal end compared with their regular nucleotide counterparts. As for the activation of phosphonates to produce their pharmacological activity, they only need two phosphorylation steps to be converted to their active diphosphate derivatives, which, akin to the triphosphate derivatives of NRTIs, serve as alternative substrates (with respect to the natural substrate 2′-deoxyadenosine triphosphate) in the reverse transcription reaction, and upon their incorporation they act as obligatory chain terminators (Figure 5).[54] Agents belonging to this class of drugs bear two negative charges that would limit their transport into cells; thus, (again) monophosphate prodrugs are being extensively investigated to improve the cellular uptake of these agents and eventually the therapeutic effect.

For example, the phosphonate derivative of 2′-fluoro-2′,3′-didehydro-2′,3′-dideoxyadenosine (**12**, Figure 6) is being developed by Gilead Sciences as a potential treatment for HIV infections.[55] As well as possessing potent anti-HIV activity, compound **12**, also known as GS-9148,[55] retained activity against multiple NRTI-resistant HIV-1 strains and more importantly exhibited low renal and mitochondrial toxicities.[56] Gilead Sciences pursued the development of this compound in the phosphonamidate form (**13**, Figure 6) to improve oral bioavailability and cellular uptake. The Gilead group has also studied the metabolism of this prodrug and identified cathepsin A as the major hydrolyzing enzyme.[57] Hence, inside the cell **13** is rapidly hydrolyzed to **12**, which is then intracellularly phosphorylated to the active diphosphate metabolite. Taken together, the data point to **13**, often referred to as GS-9131,[57] as being a promising NtRTI drug candidate for the treatment of HIV-infected individuals.

The only NtRTIs currently approved for use in patients suffering from HIV is tenofovir disoproxil fumarate (**14**), the fumarate salt of the bis(isopropoxycarbonyloxymethyl) ester of (*R*)-9-(2-phosphonylmethoxypropyl)adenine (Figure 6). Compound **14** is prescribed as a once daily dose of 300 mg. It is also available in combination with **6** in a single tablet to be taken once daily. The fixed dose of **14** (300 mg) and **6** (200 mg), now marketed as Truvada, is bioequivalent to the individual dosage forms.

The addition of **14** to the existing antiretroviral therapy regimens has given beneficial results. In a 144-week study involving 602 people with HIV, **14** (300 mg/day) was used in combination with **7** (2 × 150 mg/day) and **15** (600 mg/day), and at week 48, the HIV RNA levels in 80% of the patients were less than 400 copies/mL. For those individuals who had not previously used antiretrovirals, **14** was found to be as safe as **2** in combination with **7** and **15**. More interestingly, the **14**-based combination reduced the incidence of lipodystrophy and produced more favorable lipid profiles than the **2**-based combination.[58] In addition, no renal adverse effects were seen in antiretroviral-naive patients after 288 weeks of once-daily treatment with **14**, **7**, and **15**.[59] The results from a cumulative 3 year follow-up study looking at the combinations of compounds **14**, **7**, and **15** versus compounds **1**, **7**, and **15** proved that the combination based on **14** was superior in durability of viral load suppression and safety compared to that containing **1**.[60] Overall, a simple once-daily dosing regimen of **14**, **7**, and **15** is virologically and immunologically effective, well-tolerated, and safe with benefits in the lipid profile of the majority of the patients.[61] In 2008, compound **14** was approved for the treatment of hepatitis B.[62]

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs). The first reports on the ability of nonsubstrate analogues to inhibit the HIV reverse transcriptase appeared in 1989/1990.[63−65] These agents inhibit the HIV-reverse transcriptase by binding noncompetitively to an allosteric site located at a short distance (∼15 Å) from the catalytic site.[66,67] As well as **15**, there are three different NNRTIs, i.e., etravirine[68] (**16**), nevirapine[69] (**17**), and delavirdine[70] (**18**) (Figure 7), that have so far been formally approved for clinical use in the treatment of HIV-patients. The use of the first generation of NNRTIs, i.e., compounds **15**, **17**, and **18**, has been complicated by a rapid development of resistance especially when these compounds are used in

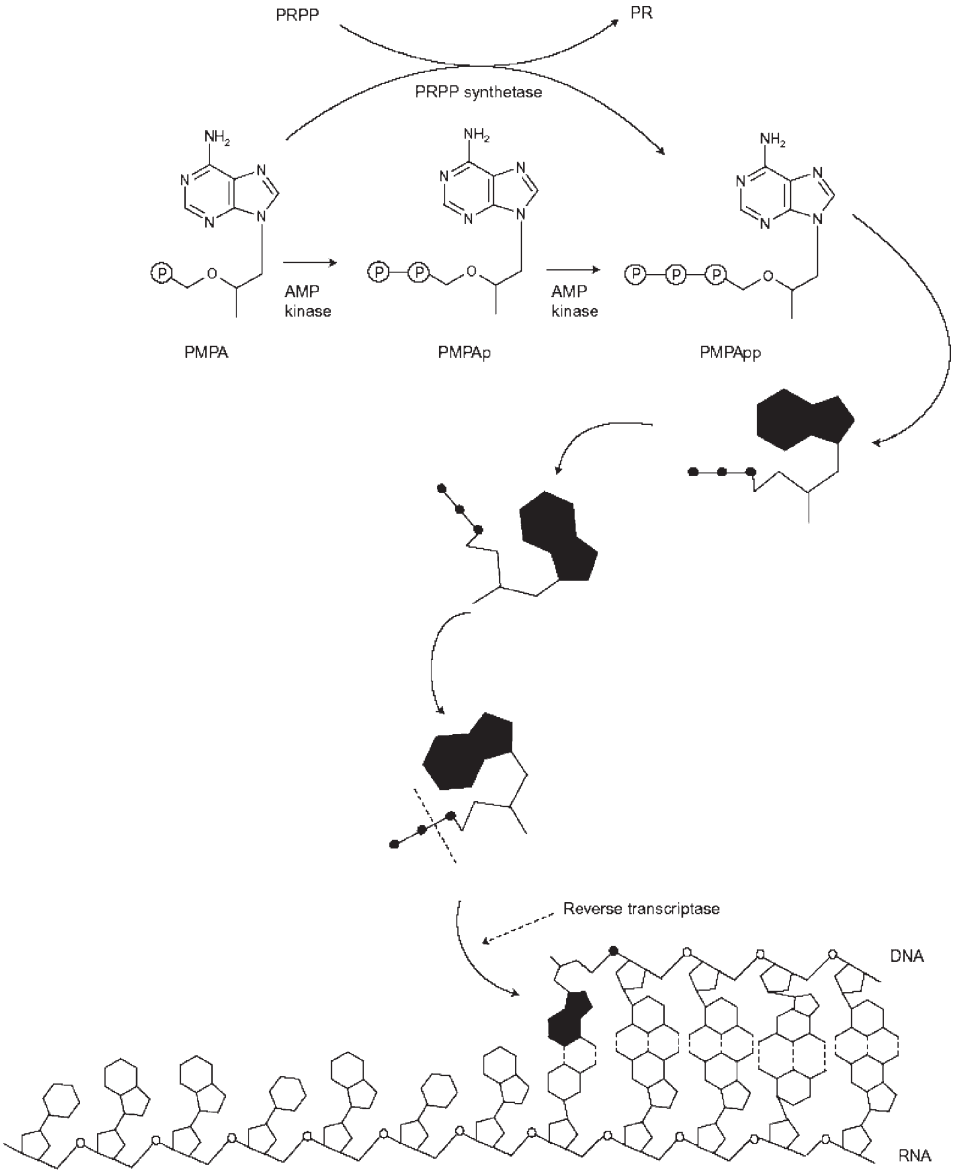

Figure 5. Activation and mechanism of action of TDF (**14**), a NtRTI. Adapted from *Expert Review of Anti-Infective Therapy* (De Clercq, E. Potential of acyclic nucleoside phosphonates in the treatment of DNA virus and retrovirus infections. *Expert Rev. Anti-Infect. Ther.* **2003**, *1* (1), 21−43)[54] with permission of Expert Reviews Ltd., Copyright 2003.

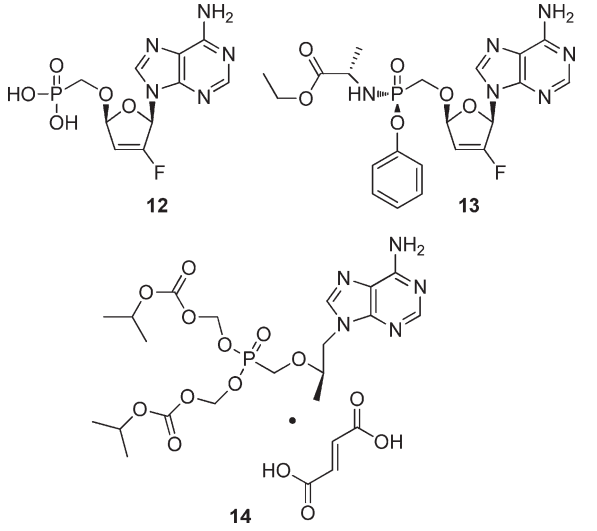

Figure 6. Structures of NtRTIs.

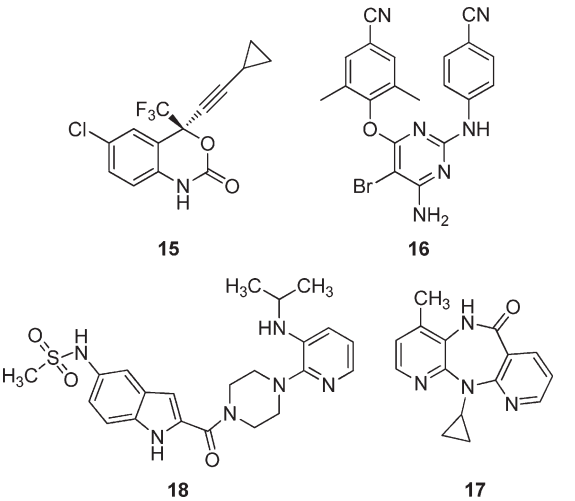

Figure 7. Structures of the currently FDA-approved anti-HIV NNRTIs.

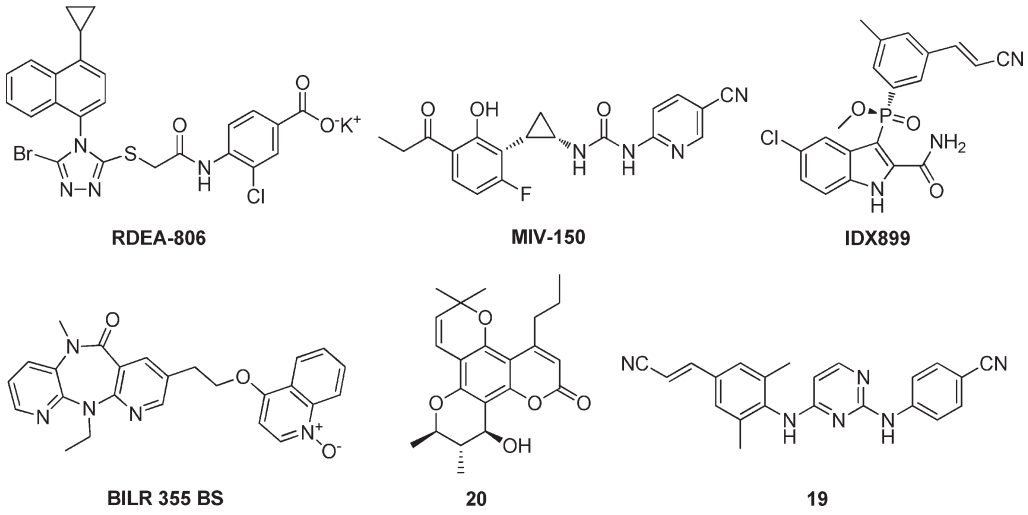

Figure 8. Structures of anti-HIV NNRTIs in clinical development (phase II or phase III).

monotherapy. In particular, the mutations Y181C and K103N in the reverse transcriptase were the most worrying, as it often led to resistance to many different NNRTIs as a result of overlapping resistance profiles.[71]

Thus, a second generation of NNRTIs was developed to address mainly the issue of drug resistant mutations. The way to achieve this was to maximize interactions not with the amino acid chains lining the allosteric binding pocket but with main-chain atoms and conserved residues of the reverse transcriptase such as W229.[72] Such approaches have led to the identification of a number of compounds that are indeed resilient to the Y181C and/or K103N mutations. Among these second generation NNRTIs is compound **16**, which was approved in 2008. It has shown potent activity against HIV-1 strains carrying the L100I, K103N, Y181C, and Y188L mutations.[73] This impressive resistance profile is believed to be a result of the increased flexibility of the molecule, which potentially gives it a greater number of binding modes in the active site.[74] Data from phase IIb studies revealed **16** to have high efficacy in patients infected with virus that had three PI resistance mutations and genotypic resistance to approved NNRTIs.[75] Notably, in patients with baseline NRTI and NNRTI resistance, treatment with a **16**-based regimen was found to be inferior to treatment with a protease inhibitor-based regimen.[76] Meanwhile, data from two large phase III studies showed that after 48 weeks the mean change in CD4 cell count was higher in the compound **16** groups compared with the control groups.[77] Since the site of action of NNRTIs is relatively close in terms of distance to the substrate binding site, NNRTIs may be assumed to interfere with the active (catalytic) site and thus to disturb the normal functioning of the reverse transcriptase. The amino acid with which the NNRTIs interact within the NNRTI-binding pocket may be prone to mutate, and this has proven to be the case for, among others, the amino acid residue lysine at position 103 (K103N) and tyrosine at position 181 (Y181C). Some newer NNRTIs that are being developed, such as rilpivirine[78] (**19**, Figure 8), seem to retain sufficient activity against the K103N and Y181C reverse transcriptase mutants. Compound **19**, which was first reported by Janssen et al. in 2005,[78] is currently undergoing phase III clinical trials as a single daily dose of 25 mg and is expected to be approved for clinical use in the very near future.[79] As well as having high potency against HIV-1 mutants resistant to other NNRTIs, compound **19** is relatively easy to synthesize and formulate and shows good oral bioavailability. Impressively, this agent exhibits long duration of activity with reports suggesting an activity lasting for 1 month after a single parenteral injection.[80]

Probably the most unique NNRTI being developed is (+)-calanolide A[81] (**20**), as it is the only anti-HIV natural product undergoing clinical trials. It is a natural product isolated from a tropical rain forest plant of the species *Calophyllum lanigerum*, which has been found to possess activity against wild-type HIV-1 (EC_{50} = 0.1 μM) and clinically isolated resistant strains such as A17 (Y181C mutant).[81,82] Although this agent has been described as a NNRTI, it is thought to have a complex mechanism of action that involves two possible binding sites: a site near both the pyrophosphate binding site and the active site of the reverse transcriptase enzyme.[83,84] Despite the relatively low potency of **20**, it was still pushed forward for clinical studies.[85−88] The development of new analogues of **20**, which have higher potency versus HIV-1, has recently been reported.[89]

In addition to compounds **19** and **20**, there are four more NNRTIs undergoing either phase II or phase III trials (Figure 8): (*R*,*E*)-methyl (2-carbamoyl-5-chloro-1*H*-indol-3-yl)(3-(2-cyanovinyl)-5-methylphenyl)phosphinate (IDX-899[90]), 1-(5-cyanopyridin-2-yl)-3-((1*S*,2*S*)-2-(6-fluoro-2-hydroxy-3-propionylphenyl)cyclopropyl)urea (MIV-150[91]), potassium 4-(2-((5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4-triazol-3-yl)thio)acetamido)-3-chlorobenzoate (RDEA806[92]), and 4-(2-(11-ethyl-5-methyl-6-oxo-6,11-dihydro-5*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-8-yl)ethoxy)-quinoline 1-oxide (BILR 355 BS[93]).[94]

Protease Inhibitors (PIs). The HIV protease is responsible for the cleavage of the gag and gag-pol precursor polyproteins to the structural proteins (p17, p24, p7, p6, p2, p1) and the functional proteins [protease(p11), reverse transcriptase (p66/p51), and integrase (p32)], thereby securing maturation and infectivity of the progeny virions.[95] HIV protease inhibitors will interfere with this late stage of the viral replication cycle and prevent the formation of infectious virus particles. Structurally, the HIV protease is a noncovalent homodimer that acts catalytically as an aspartic acid protease. The active site is located at the dimer interface and possesses catalytic Asp residue from each monomer: D25 and D125.[96]

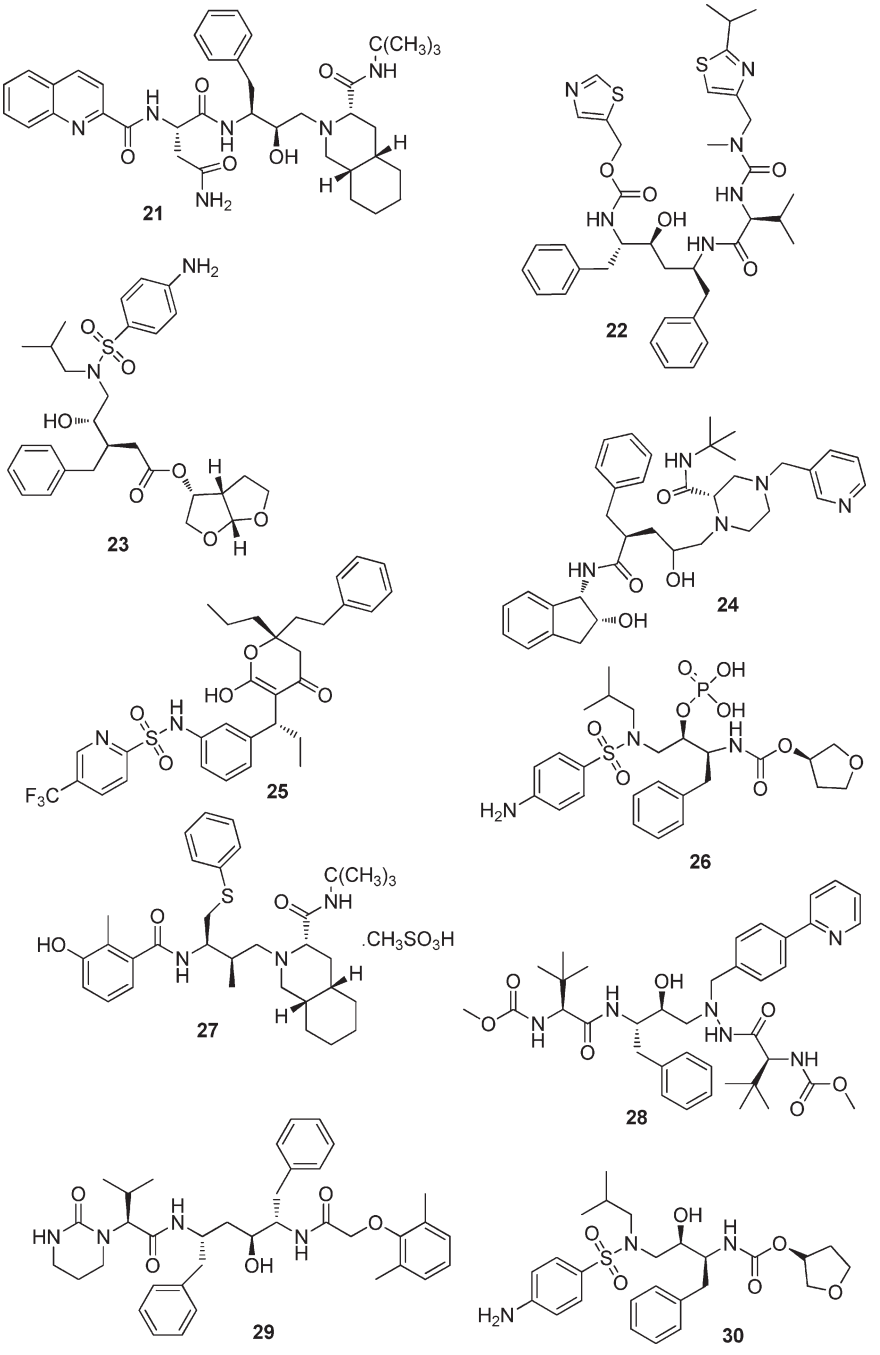

Figure 9. Structures of the currently FDA-approved anti-HIV protease inhibitors (PIs).

There are currently 10 FDA-approved protease inhibitors: saquinavir[97] (**21**), ritonavir[98] (**22**), darunavir[99] (**23**), indinavir[100] (**24**), tipranavir[101] (**25**), fosamprenavir[102] (**26**), nelfinavir[103] (**27**), atazanavir[104] (**28**), lopinavir/ritronavir[105] (**29**), and amprenavir[106] (**30**) (Figure 9). With the exception of **25**, all the approved PIs are peptidomimetic transition-state analogues that contain a nonhydrolyzable transition state isostere. As drug molecules with peptide character, these agents have the classic problem of peptide-based drugs, which is their poor bioavailability. Furthermore, this class of drugs suffers from the ever-present problem of resistance and cross-resistance as well as having a specific toxicity profile (i.e., lipodystrophy). This has prompted the search for new, nonpeptidic inhibitors of HIV-protease, with cyclic urea, 4-hydroxycoumarin, L-mannaric acid, or 4-hydroxy-5,6-dihydro-2-pyrone as the central scaffold instead of the peptidomimetic hydroxyethylene,[107,108] e.g., compound **25**. This last compound shows little cross-resistance with the peptidomimetic inhibitors.

One of the recent HIV protease inhibitors approved for the treatment of HIV-positive individuals is compound **28**. This agent combines a favorable resistance profile distinct from that of the other protease inhibitors, with a favorable pharmacokinetic profile allowing once-daily dosing. Compounds **21**, **27**, and **30** resistant HIV-1 strains remained sensitive to **28**, while compounds **22** and **24** resistant viruses showed 6- to 9-fold changes in sensitivity to **28**. Conversely, **28**-resistant (N88S, I84V) virus, selected upon repeated passage of the virus in the presence of the compound, remained sensitive to **21** but showed various degrees of

cross-resistance to compounds **22**, **24**, **27**, and **30**.[109] Compound **28** appeared to have a resistance profile that is distinct from that of the other HIV protease inhibitors. Analysis of the genotype profiles of 943-PI-susceptible and -resistant clinical isolates identified a strong correlation between the presence of the amino acid changes at specific residues (10I/V/F, 20R/M/I, 24I, 33I/F/V, 36I/L/V, 46I/L, 48V, 54V/L, 63P, 71V/T/I, 73C/S/T/A, 82A/F/S/T, 84V, and 90M) and decreased susceptibility to **28**. While no single substitution or combination of substitutions was predictive of **28** resistance (< 3-fold reduction in susceptibility), the presence of at least five of these substitutions correlated strongly with loss of **28** susceptibility.[110]

In high antiretroviral-experienced patients, once-daily **28** showed good activity when combined with two NRTIs.[111] In addition, once-daily **28** (200, 400, or 500 mg) rapidly and durably suppressed HIV RNA levels and durably increased CD4 cell counts. Furthermore, it was not associated with clinically relevant increases in total cholesterol, fasting low density lipoprotein (LDL) cholesterol, or fasting triglycerides.[112,113]

It is worth noting that there are important pharmacokinetic issues relating to the use of protease inhibitors particularly when used in combinations. For example, compound **22** is a powerful inhibitor of the cytochrome P450 metabolic pathway,[114] which is responsible for the metabolism of many drugs such as **21**, **24**, analgesics, antidepressants, and various antiarrythmics,[115] and thus combining **22** with these drugs results in higher increases in plasma concentrations, which may lead to fatal consequences.

Fusion Inhibitors (FIs). One of the key steps in the infection of the host cells by HIV is the interaction between the virion glycoprotein gp120 on the outer membrane and the CD4 receptor on the host cell surface. This results in conformational changes that lead to the unmasking of a second gp120-binding site for target chemokine co-receptors CXCR4 and CCR5 and binding of gp120 to either or both co-receptors. The establishment of the co-receptor binding leads to the fusion-active conformation of the viral transmembrane fusion protein gp41. Structurally, the gp41 ectodomain has two main heptad repeat regions: HR1 (proximal to the N terminus) and HR2 (proximal to the C terminus). The hydrophobic region of the fusion peptide is inserted into the cell membrane, while a trimeric-coiled coil structure is formed by the HR1 regions of the gp41. The HR2 region then folds back within the hydrophobic grooves of the HR1 coiled coil, forming a hairpin structure containing a thermodynamically stable six-helix bundle that draws the viral and cellular membranes together for fusion.[116]

Numerous synthetic peptides derived from gp41 were used in investigational studies aimed at vaccine development but were not designed and targeted as HIV-1 fusion inhibitors. Nevertheless, these agents showed appreciable antiviral activity. The first synthetic peptide mimetic that possessed good anti-HIV activity was DP-107[117] (structure not disclosed). This agent is a 38-amino acid molecule corresponding to gp160 residues 558−595, the N-terminal region of gp41.[117] However, studies at the C-terminus of gp41 led to the identification of a 36-amino acid peptide DP-178[118] (**31**) (structure not disclosed), which showed potent anti-HIV activity.[119] Compound **31**, also known as enfuvirtide, then became the first and so far the only HIV-1 fusion inhibitor approved for use in HIV-positive individuals. One of the early clinical studies on **31** was a 14-day trial using it as monotherapy in 16 patients.[120] This drug was administered in the form of intravenous infusions at a dose range of 3−100 mg (3, 10, 30, and 100 mg), twice daily. At the highest dose (100 mg, twice daily), there was a 1.5- to 2.0-fold reduction in plasma HIV RNA by day 15. Meanwhile, two phase III clinical studies have indicated that **31** provided a significant antiretroviral and immunological benefit following a 24-week treatment period. These findings were later confirmed by a 48-week study.[121−123] Compound **31** has to be administered twice daily by subcutaneous injection. This inevitably leads to injection site reactions including erythema, induration, nodules, and cysts. Another inevitable problem is the cost of production of a 5000 Da molecular mass peptide.[124] In terms of virus drug resistance, mutations G36D and V38A within the GIV stretch at positions 36−38 of the amino terminal heptad motif of gp41[125] and also other mutations seem to emerge promptly in patients upon monotherapy with **31**.[126]

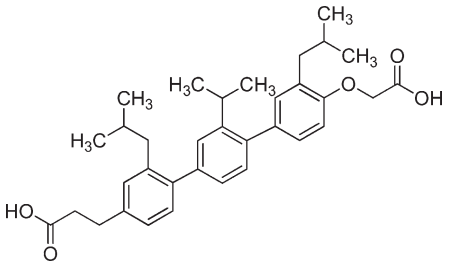

Figure 10. Structure of terphenyl derivative, a potential new HIV fusion inhibitor.

Recently, a new strategy based on α-helix mimicry targeted at gp41 and aimed at inhibiting virus-cell fusion has been described.[127,128] Tris-functionalized 3,2′,2″- terphenyl derivatives could serve as effective mimics of the exposed N-helical regions of the transient gp41 intermediate and thus potentially trap this structure prior to six-helix bundle formation, which is required for virus−cell fusion. The terphenyl derivative (Figure 10) was indeed found to inhibit HIV-1 mediated cell-to-cell fusion but only at a relatively high concentration ($IC_{50} \approx 15$ μg/mL).[128] A similar approach, based on short constrained peptides (i.e., C14 linkmid),[129] also resulted in inhibition of cell-to-cell fusion ($IC_{50} = 35$ μM).

Co-Receptor Inhibitors (CRIs). One of the key reactions that eventually allow virus−cell fusion involves chemokine receptors. There are several types of these receptors, but from studies performed on HIV-1 clinical isolates, the two major co-receptors are CCR5 and CXCR4.[130,131] CXCR4 is the receptor for T-lymphotropic (or X4) HIV strains, whereas CCR5 is the co-receptor for macrophage (M)-tropic (or X5) HIV strains. CXCR4 normally functions as the receptor for the chemokine SDF-1 (stromal cell derived factor), and CCR5 does so for RANTES (regulated upon activation, normal T-cell expressed, and secreted) and MIP-1α and MIP-1β (macrophage inflammatory proteins), and accordingly, these chemokines inhibit the infectivity of X4 and X5 HIV strains, respectively.[95]

Numerous small molecular weight CXCR4 and CCR5 antagonists have been identified (Figure 11). The prototype of the CXCR4 antagonists (inhibitors) is the bicyclam AMD3100[132] (**32**), which was shown to inhibit T-tropic HIV strains by selective antagonism of the SDF-1 chemokine receptor CXCR4.[132,133] Within the HIV life cycle, **32** was found to interfere with the binding of HIV gp120 to the CXCR co-receptor after it is bound to the CD4 receptor and

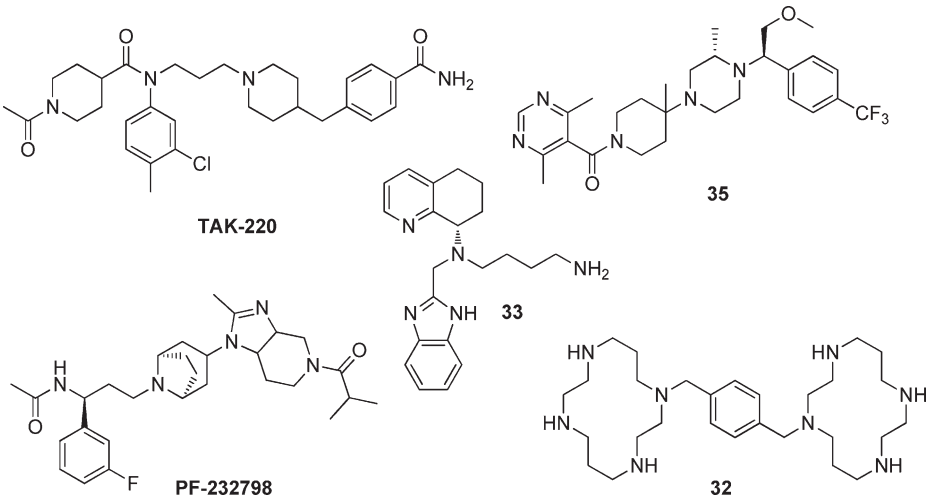

Figure 11. Structures of some CRIs with potent anti-HIV activity.

before the HIV gp41 initiates the fusion of the virus envelope membrane with the cell membrane.[134,135] Compound **32** has been shown to have antiviral activity in SCID-hu Thy/Liv mice infected with a CXCR4 using clinical HIV isolates,[136] and proof of concept that it is also effective in a patient infected with an X4 HIV-1 strain has been provided.[137] During phase I clinical studies, it was found that **32** caused significant enhancement of the white blood cell count in human volunteers.[138] This compound was further investigated for stem cell mobilization and transplantation in patients with multiple myeloma or non-Hodgkin lymphoma.[139] Further details on the development of **32** as a stem cell mobilizer can be found in ref 140. A non-bicyclam derived from **32**, AMD070[141] (**33**), has been identified as a potent ($EC_{50} \approx 1-10$ nM), orally bioavailable CXCR4 antagonist.[141,142] Compound **33**, which is currently in phase II clinical trials, has been shown to selectively inhibit X4-tropic virus in HIV-1 infected patients.[143,144] The possibilities of **33** having a stem-cell mobilizing effect or being able to exert an inhibitory effect on other CXCR4-mediated processes remain subject to further investigations.

Currently, maraviroc[145] (**34**, Figure 12) is the only CCR5 antagonist that has been approved for the treatment of HIV. This compound was shown to have excellent potency both in vitro and in vivo.[146,147] Notably, 100 mg of **34** twice daily resulted in viral load suppression for at least 10 days after therapy, suggesting that treatment with **34** may be based on infrequent administration, i.e., once weekly instead of once daily.[148] Among the CRIs in advanced clinical trials is vicriviroc[149] (**35**, Figure 11), which is expected to be approved in the very near future. In a 14-day monotherapy trial in HIV-infected adults, **35** resulted in a significant decrease of HIV in HIV-infected subjects,[150] while it was also found to cause significant viral suppression in a 24-week combined therapy in treatment-experienced patients.[151] Compound **35** is currently undergoing two phase III clinical trials. In addition to **35**, 1-acetyl-*N*-(3-(4-(4-carbamoylbenzyl)piperidin-1-yl)propyl)-*N*-(3-chloro-4-methylphenyl)piperidine-4-carboxamide (TAK-220)[152] and *N*-((1S)-1-(3-fluorophenyl)-3-((1*R*,5*S*)-3-(5-isobutyryl-2-methyl-3a,4,5,6,7,7a-hexahydro-1*H*-imidazo[4,5-*c*]pyridin-1-yl)-8-azabicyclo[3.2.1]octan-8-yl)-propyl)acetamide (PF-232798)[153] are two more CRIs that appear to be promising candidates for further development (Figure 11).

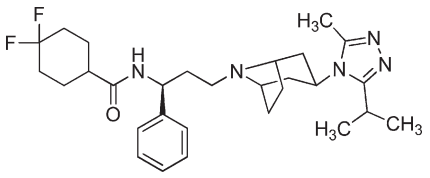

Figure 12. Structure of maraviroc, the only CRI approved for HIV treatment.

There are, however, some concerns regarding the use of CRIs as treatment of HIV, as it is thought that such drugs may contribute toward the emergence of resistant HIV-1 strains.[154]

Integrase Inhibitors (INIs). The integration of the proviral DNA into the host cell chromosomal DNA is an essential step in the viral replication cycle. The enzyme that catalyzes this process, i.e., integrase, is considered to be one of the most promising new targets in preclinical or early clinical trials.

The HIV integrase is a 32 kDa protein comprising three structural domains: (1) the aminoterminal domain (NTD), (2) a catalytic core domain (CCD), and (3) the carboxyl-terminal domain (CTD).[155] Similar to other integrases found in DNA transposases and retrotransposases, a key component of the catalytic core of HIV-integrase is the highly conserved DDE motif which is composed of three amino acids: D64, D116, and E152.[155] These three conserved residues are very critical for the activity of the enzyme, as they have been found to bind to a divalent metal cofactor (Mg^{2+} or Mn^{2+}).[156] Although the CCD domain is the one that contains the catalytic part of the enzyme, the NTD and CTD are essential for the full activity of the enzyme. Indeed, it has been established that in order for the HIV-integrase to catalyze the 3′-processing and strand transfer, which are the main functions of this enzyme, the CCD needs both the NTD and CTD in a dimeric complex.[157]

The key functions of the HIV integrase are the 3′-end processing and strand transfer or integration.[155,158] The first of these two functions takes place after the reverse transcription, as the formed cDNA is primed for integration in the cytoplasm by integrase-mediated trimming of the 3′-ends of the viral DNA. This is achieved when the integrase binds to the double strand viral DNA as it is being reverse-transcribed to form a preintegration complex. It then cleaves two

terminal nucleotides from each of the 3′-ends of the DNA in the conserved CA-rich region (3′-end processing). This 3′-processing phenomenon requires both fully functional integrase and the integrity of the last 10−20 base pairs at both ends of the viral DNA. The preintegration complex is then shuttled into the nucleus, where the processed 3′ ends of the viral DNA are directly inserted into the cellular DNA phosphodiester backbone through a pair of transesterification reactions (strand transfer or integration). The two overhanging 5′-end nucleotides are cleaved, and the target DNA is then integrated into cellular DNA.

At the moment, there is only one FDA-approved HIV-integrase inhibitor, raltegravir[159] (**36**, Figure 13), and one more, elvitegravir (**37**, Figure 13), is now entering phase III clinical trials. Compound **36** is available in 400 mg tablets (to be taken twice daily) and is only licensed for use in combination with other anti-HIV drugs. In a recent published 48-week study involving 198-naive patients with plasma HIV 1 RNA levels of ≥5000 copies/mL, it was shown that treatment with **36** at 100, 200, 400, and 600 mg twice daily versus **15** at a dose of 600 mg/d, all in combination with **14** at a dose of 300 mg/d and with **7** at a dose of 300 mg/d, resulted in 85−98% of the patients having their plasma HIV-1 RNA levels lowered to less than 400 copies/mL.[160] In fact, these low levels of HIV-1 RNA were achieved after 24 weeks of treatment and were sustained until the end of the study (week 48). After 24 and 48 weeks of treatment, compound **36** did not result in increased serum levels of total cholesterol, LDL cholesterol, or triglycerides. It is worth noting that five (3%) patients on **36** and one patient on **15** experienced virologic failure before week 48 and drug-related clinical adverse events were less common with **36** than with **15**.

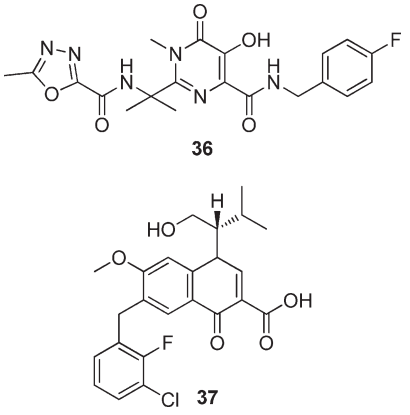

Figure 13. Structures of raltegravir (**36**) and elvitegravir (**37**).

Compound **37** is an integrase inhibitor that is currently undergoing phase III clinical trials. This agent showed good bioavailability in rats and dogs, 34% and 30%, respectively, while its administration in combination with the protease inhibitor **22** resulted in a 20-fold increase in oral bioavailability.[161] Further studies have also noted **37** to be highly effective in reducing viral loads.[162−164] A triple mutation, i.e., T66I, L74M, and S230R, in the integrase has been found to be the cause of resistance to this class of drugs.[165]

Although, as discussed above, we now have a good collection of anti-HIV drugs that has transformed HIV/AIDS from a fatal to chronic manageable disease, there is still room for improvement. This could be done by the discovery of new anti-HIV drugs that address the issues of the currently used classes of anti-HIV drugs, e.g., resistance, and/or discovery of new agents with novel mechanisms of action. There is no doubt that current drug development programs aimed at discovering new agents that belong to the already existing classes of anti-HIV drugs are still needed to deliver drugs that benefit AIDS patients. Nevertheless, the second option of discovering new drugs with novel mechanisms of action would be of greater benefit, as they would contribute toward overcoming (some of) the current resistance mechanisms, which would eventually make it easier to issue a broader combinations of anti-HIV drugs.

A quick glance at the various anti-HIV drugs that are currently undergoing phase II or phase III of clinical trials (Table 2) reveals that the majority of them inhibit enzymes for which we already have drugs approved. However, these agents are the "next generation" of the currently used drugs, since they seem to have better activity against drug-resistant virus strains as well as better resistance and/or toxicity profiles. In addition, most of these agents are being investigated as possible once-daily pills, which, if approved, would enhance the drug compliance of HIV patients. One of the

Table 2. List of Anti-HIV Drugs Currently Undergoing Clinical Trials (Phase II or Phase III)

drug	class	developer	phase
apricitabine	NRTIs	Avexa	III
amdoxovir	NRTIs	RFS Pharm	II
elvucitabine	NRTIs	Achillion Pharmaceuticals	II
racivir	NRTIs	Pharmasset	II
BILR 355 BS[93]	NNRTIs	Boehringer Ingelheim	II
(+)-calanolide A	NNRTIs	Sarawak MediChem Pharmaceutics	II
IDX899[90]	NNRTIs	Idenix Pharma	I/II
MIV-150[91]	NNRTIs	Medivir, Chiron	II
RDEA806[92]	NNRTIs	Ardea	II
rilpivirine	NNRTIs	Tibotec	IIb
AK-602[166]	CRIs	Kumamoto University	III
AMD070[141]	CRIs	AnorMed	II
HGS004[167] (structure not disclosed)	CRIs	Human Genome Sciences	II
ibalizumab (TNX-355)[168] (structure not disclosed)	CRIs	TailMed Biologics	II
PF-232798[153]	CRIs	Pfizer	II
VCH-286[171] (structure not disclosed)	CRIs	ViroChem Pharm	II
vicriviroc	CRIs	Schering Plough	III
PRO 140[169] (structure not disclosed)	FIs	Progenics	II
SP01A[170] (structure not disclosed)	EI	Samaritan Pharmaceuticals	III
elvitegravir	INIs	Gilead Sciences	III

Table 3. List of the Currently FDA-Approved Anti-HIV Drug Combinations

combination	components	manufacturer	date of FDA approval
Combivir	zidovudine (300 mg), lamivudine (150 mg)	GlaxoSmithKline	September 27, 1997
Trizivir	abacavir (300 mg), lamivudine (150 mg), zidovudine (300 mg)	GlaxoSmithKline	November 14, 2000
Epzicom (U.S.) or Kivexa (Europe)	abacavir (600 mg), lamivudine (300 mg)	GlaxoSmithKline	August 2, 2004
Truvada	tenofovir disoproxil fumarate (300 mg), emtricitabine (200 mg)	Gilead Sciences	August 2, 2004
Atripla	TDF (300 mg), emtricitabine (200 mg), efavirenz (600 mg)	Bristol-Myers Squibb, Gilead Sciences	July 12, 2006

exciting elements that comes out of Table 2 is that a significant number of potential drugs belong to relatively newer classes of drugs such as co-receptor inhibitors, fusion inhibitors, and entry inhibitors. Agents belonging to this class of drugs have undoubtly enriched the number of anti-HIV drugs used in the clinics and also contributed greatly to the continuous fight against HIV. Thus, it could be predicted that drugs acting at the first stages of the HIV life cycle would be among the largest classes of anti-HIV approved drugs within the next 20 years.

Probably the most disappointing reading from Table 2 would be regarding the development of anti-HIV drugs derived from natural products. Although there has been an interest in anti-HIV natural products,[172] compared to anticancer agents derived from natural products, the development of anti-HIV drugs from natural products seems to be lagging behind. Apart from **20**, which itself is not extremely potent versus HIV-1, an increased focus on the development of plant-derived anti-HIV drugs would be desirable.

As mentioned earlier, the development of anti-HIV drugs with novel mechanisms of action should be a high priority for everyone involved in anti-HIV drug development. A number of new targets for anti-HIV drug discovery have been identified.[173] One of these targets are HIV regulatory and/or accessory proteins such as Tat, Rev, and Nef. These proteins are essential for the functioning of HIV, and thus inhibiting their action might be a beneficial strategy for the fight against HIV.[174−176] Also, inhibiting HIV ribonuclease H (RNase H) as a means of developing novel anti-HIV agents has been a topic that is picking up a lot of interest lately.[176] A number of small molecules have been identified as inhibitors of RNase H.[177,178] Another exciting and relatively new strategy for combating HIV is the development and use of carbohydrate-binding agents (CBAs).[179,180] These agents are thought to possess a dual mechanism of action, first, through binding to the glycans of the viral envelope and subsequently blocking virus entry and, second, through indirect (additional) antiviral action resulting from the progressive creation of deletions in the envelope glycan shield, which triggers the immune system to act against previously hidden immunogenic epitopes of the viral envelope.[180] A series of compounds have already been described as potent anti-HIV agents that act as CBAs.[181−183] In addition to the strategies discussed above, designing new drugs that enhance the host cell defense should also be high in the priority list of medicinal chemists.

Anti-HIV Drug Combinations

The introduction of combination therapy in the mid-1990s, termed highly active antiretroviral therapy (HAART), has significantly decreased the morbidity and mortality rates of HIV patients[184−187] and has certainly made HIV monotherapy as belonging to the past. Indeed, nowadays HIV/AIDS therapy guidelines stress the use of combination therapy, which includes two or three (or more) drugs that target more than one step of the virus life cycle. Overall, the use of HAART in the mid-1990s resulted in patients taking a lot of tablets, so to increase compliance and adherence, drug companies have been working tirelessly to design single formulations that contain more than one drug. Such efforts led to the development and approval of currently five anti-HIV drug combinations (Table 3).

The first to be approved was Combivir, which consisted of two NRTIs, **1** (300 mg) and **7** (150 mg), and is taken as one tablet twice daily. Three years later, Trizivir, which is given as one tablet twice daily and consists of three different drugs, was approved. These drugs are compounds **5** (300 mg), **7** (150 mg), and **1** (300 mg), which are all NRTIs. In 2004, two more anti-HIV drug combinations, Epzicom and Truvada, were approved. Epzicom consists of 600 mg of **5** and 300 mg of **7**. In Europe this formulation is marketed under the name Kivexa. Truvada is the first drug combination to include a NtRTI. Indeed, it includes compounds **14** (300 mg) and **6** (200 mg). In 2006, the fifth anti-HIV drug combination, Atripla, which consists of Truvada plus **15** (600 mg), was approved. The availability of these drug combinations has changed anti-HIV drug treatment from taking more than 10 pills a day to 1 tablet pill daily. This, as a result, has improved the adherence to medication, lowered drug resistance development, and improved the quality of lives of HIV-positive individuals.

Prophylaxis of HIV with Tenofovir Disoproxil Fumarate (14)?

The use of compound **14** in the prophylaxis of HIV infections is continuing to excite attention. The initial observation regarding the possibility of the role that **14** can play in the prevention of retrovirus infections appeared in 1995. Tsai et al.[188] observed complete protection of macaques against intravenous simian immunodeficiency virus infection as a result of subcutaneous once daily administration of tenofovir (the active ingredient of **14**) starting 48 h before, 4 h after, or 24 h after inoculation and continuing for 4 weeks. Following this study, two other reports appeared in the literature, both having the same message about the ability of **14** to exert preventive activity against retrovirus infections.[189,190] However, a more recent study in which **14** was orally dosed for 14 weeks either daily or weekly to rhesus macaques repeatedly given rectal challenges with simian human immunodeficiency virus (SHIV) revealed that **14** provided partial protection against SHIV infection but ultimately did not protect all **14**-treated animals against multiple virus challenges.[191] Although the combination of **14** with **6**, both administered subcutaneously, completely prevented rectal SHIV transmission in macaques,[192] recent data showed that the combination of

compounds **14** and **6** as a prophylactic regimen needs further investigation.[193]

These findings highlight the need for further investigations into the role of **14** in preventing retroviral infections. Already published reports demonstrate the ability of **14** to prevent retrovirus infections. Combining these findings with the safety/efficacy profile of **14**, which has been established from its use in the treatment of AIDS in humans since its approval in 2001, compound **14** could be strongly recommended in the pre- and postexposure prophylaxis of HIV infection in humans.

The wide-scale prophylactic use of **14** to prevent HIV infections might, however, raise a few issues: (1) risk for long-term toxicity, (2) emergence for virus-drug resistance, and (3) stimulation of promiscuity. These concerns, however, could be counteracted by the following arguments:[194] First, compound **14** has proved to be relatively free of side effects (i.e., kidney toxicity and bone demineralization). Second, emergence of HIV resistance to **14** has not proven to be a significant problem in HIV-infected individuals, where there is a continuous exposure of the virus to the compound.[195−197] Third, the fear that the wide-scale use of **14** might stimulate promiscuity in the sense of increased homo- or heterosexual contacts or parenteral drug abuse should by no means detract from the protection offered by **14** in preventing unwanted HIV infections in individuals who are unwillingly exposed to them.

Conclusion

There is no doubt that, since the discovery of HIV 26 years ago, the progress made toward developing effective anti-HIV therapies has superseded that of any other (antiviral) drug discovery initiative. This unprecedented progress generated an armamentarium of anti-HIV drugs, which target several different stages of the HIV life cycle. This, therefore, has enabled the use of combination therapy in combating HIV infections. Although the drugs making up these treatment regimens have proved effective, some problems such as toxicity and resistance development have limited their use and prompted the search for new agents. The pipeline of anti-HIV drugs is well stocked with drugs that are going to be "next-generation" drugs. However, as we highlighted in this work, future anti-HIV drug research efforts should also focus on new HIV targets such as HIV proteins and RNase H. In addition, the development of anti-HIV drugs derived from natural products is an area of research where a lot of efforts should be dedicated in the future.

Biographies

Youcef Mehellou received his Ph.D. from Cardiff University (U.K.) in 2008. His Ph.D. project, which was under the supervision of Prof. Christopher McGuigan, was on the design and synthesis of novel nucleoside and nucleotide phosphoramidates as potential antiviral therapeutics. Prior to Cardiff, Youcef was a student at the Department of Pharmacy of King's College London, where under the supervision of Prof. Robert C. Hider he conducted some research on the discovery of iron chelators as possible treatments for Alzheimer's and Parkinson's diseases. Currently, Youcef is a Research Associate with Prof. Sidney M. Hecht at Arizona State University. Youcef's research interests are in nucleoside chemistry, small molecule RNA-targeting therapeutics, and the total synthesis of therapeutically useful natural products.

Erik De Clercq, M.D., Ph.D., had been teaching courses in Cell Biology, Biochemistry, and Microbiology at the Katholieke Universiteit Leuven (and Kortrijk) Medical School and was Chairman of the Department of Microbiology and Immunology until September 2006. He is currently active Emeritus Professor, President of the Rega Foundation and a Director of the Belgian (Flemish) Royal Academy of Medicine, a Member of the Academia Europaea, and Fellow of the American Association for the Advancement of Science. He is an honorary doctor of several universities (i.e., Ghent, Athens, Ferrara, Shandong, Prague, and České Budějovice). In 2008, he was elected European Inventor of the Year (Lifetime Achievement Award). He is the (co)inventor of a number of antiviral drugs (valaciclovir, brivudin, cidofovir, adefovir dipivoxil, and tenofovir disoproxil fumarate).

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