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Review

Anti-HIV drugs: 25 compounds approved within 25 years after the discovery of HIV☆

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Integrase inhibitors

ABSTRACT

In 2008, 25 years after the human immunodeficiency virus (HIV) was discovered as the then tentative aetiological agent of acquired immune deficiency syndrome (AIDS), exactly 25 anti-HIV compounds have been formally approved for clinical use in the treatment of AIDS. These compounds fall into six categories: nucleoside reverse transcriptase inhibitors (NRTIs: zidovudine, didanosine, zalcitabine, stavudine, lamivudine, abacavir and emtricitabine); nucleotide reverse transcriptase inhibitors (NtRTIs: tenofovir); non-nucleoside reverse transcriptase inhibitors (NNRTIs: nevirapine, delavirdine, efavirenz and etravirine); protease inhibitors (PIs: saquinavir, ritonavir, indinavir, nelfinavir, amprenavir, lopinavir, atazanavir, fosamprenavir, tipranavir and darunavir); cell entry inhibitors [fusion inhibitors (FIs: enfuvirtide) and co-receptor inhibitors (CRIs: maraviroc)]; and integrase inhibitors (INIs: raltegravir). These compounds should be used in drug combination regimens to achieve the highest possible benefit, tolerability and compliance and to diminish the risk of resistance development.

1. Introduction

Within 2 years after acquired immune deficiency syndrome (AIDS) had been identified as a disease in 1981, human immunodeficiency virus (HIV) [originally called lymphadenopathy-associated virus (LAV) and human T-lymphotropic virus type III (HTLV-III), HTLV-I and -II being human T-leukaemic viruses type 1 and 2] [1,2] was isolated as the putative cause of the disease. This launched an intensive search for compounds that would inhibit infectivity and replication of the virus and, hopefully, favourably alter the course of the disease. The first compound shown to inhibit HIV replication both in vitro (cell culture) and in vivo (HIV-infected individuals) was suramin [3,4]. However, the first anti-HIV agent to be licensed for clinical use (in 1987) was zidovudine. It was first described in 1985 as an antiviral agent inhibiting the infectivity and cytopathic effect of HTLV-III/LAV in vitro [5].

In these early days of anti-HIV drug research, it could hardly be foreseen that within 25 years of the virus being discovered we would now, in 2008, have at hand 25 anti-HIV compounds licensed (thus formally approved) for the treatment of AIDS (Table 1). These compounds fall within different categories depending on the target within the HIV replicative cycle they interact with (Fig. 1). The targets that have been envisaged most intensively are: reverse transcription, catalysed by reverse transcriptase (RT) (RNA-dependent DNA polymerase), a specific viral enzyme that retrotranscribes the viral single-stranded RNA genome to double-stranded proviral DNA; and proteolytic processing by the viral protease, which cleaves the precursor viral polyprotein into smaller mature (both structural and functional) viral proteins. Other targets that have been recognised more recently as sites for therapeutic intervention are viral entry, particularly virus–cell fusion and interaction of the virus with its (co-)receptors, and integration of the proviral DNA into the host cell genome, a process carried out by a specific viral enzyme, integrase, which determines whether the HIV-infected cell and all daughter cells stemming thereof will permanently carry the provirus.

2. Nucleoside reverse transcriptase inhibitors (NRTIs)

The RT associated with HIV is actually the target for three classes of inhibitors: nucleoside RT inhibitors (NRTIs); nucleotide

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RT inhibitors (NtRTIs); and non-nucleoside RT inhibitors (NNRTIs). The NRTIs and NtRTIs interact with the catalytic site (that is the substrate-binding site) of the enzyme, whereas the NNRTIs interact with an allosteric site located at a short distance (ca. 15 Å) from the catalytic site (Fig. 2).

For the NRTIs and NtRTIs to interact with the substrate-binding site they need to be phosphorylated to, respectively, the triphosphate and diphosphate forms. There are at present (in 2008) seven NRTIs that have been formally approved for the treatment of HIV infections: zidovudine (AZT); didanosine (ddI); zalcitabine (ddC); stavudine (d4T); lamivudine (3TC); abacavir (ABC); and

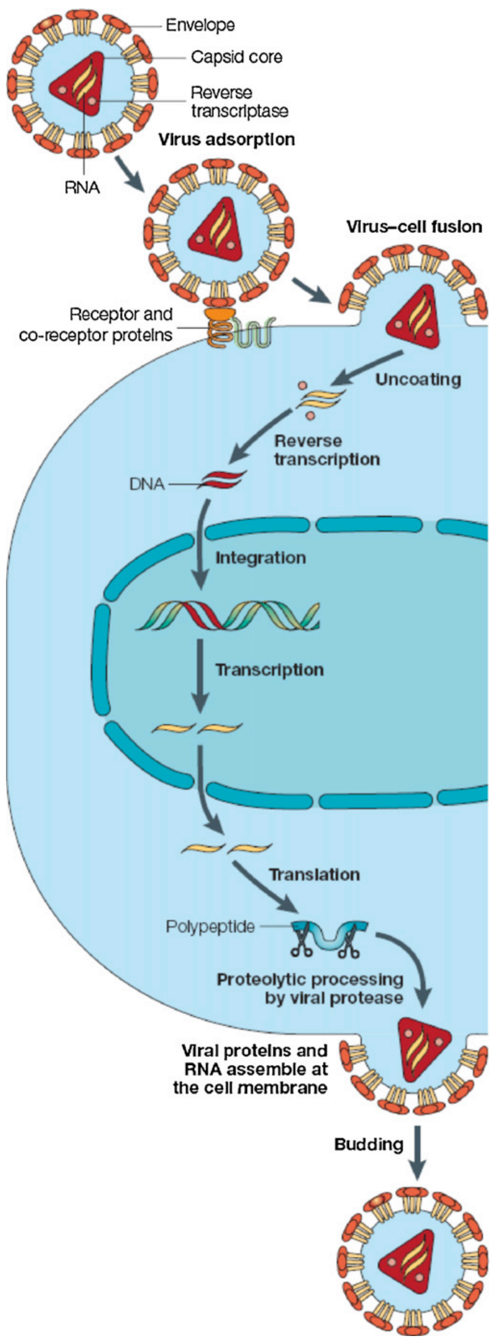


Fig. 1. Replicative cycle of human immunodeficiency virus (HIV), highlighting the principal targets for therapeutic intervention: (co-)receptor interaction; virus–cell fusion; reverse transcription (by reverse transcriptase); integration; and proteolytic processing (by viral protease). According to De Clercq [6].

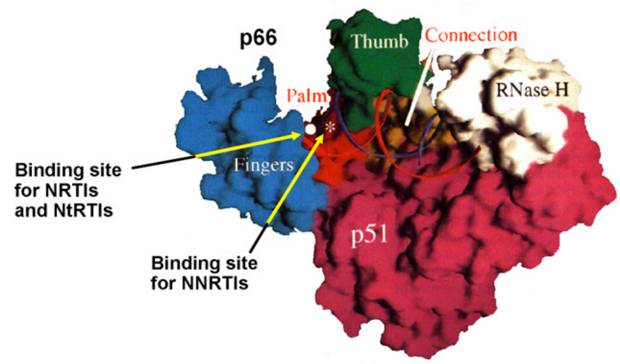


Fig. 2. Human immunodeficiency virus (HIV) reverse transcriptase with the binding site for the nucleoside reverse transcriptase inhibitors (NRTIs) and nucleotide reverse transcriptase inhibitors (NtRTIs) and the binding site for the non-nucleoside reverse transcriptase inhibitors (NNRTIs). According to De Clercq [7]; structure of the enzyme according to Tantillo et al. [8].

emtricitabine ((-)FTC) (Fig. 3). All the NRTIs can be considered as 2',3'-dideoxynucleoside (ddN) analogues and act in a similar fashion. After they have been taken up by the cells, they are phosphorylated to their 5'-monophosphate, 5'-diphosphate and 5'-triphosphate form following the same mechanism (ddN → ddN-MP → ddNDP → ddNTP) before the latter will then act as a competitive inhibitor/alternate substrate of the normal deoxynucleoside triphosphate (dNTP) substrate (either dATP, dTTP, dGTP or dCTP). Specifically, AZT and d4T are converted to dTTP competitors, ddC, 3TC and (-)FTC are converted to dCTP competitors, ddI to a dATP competitor and ABC to a dGTP competitor, according to the following pathways: AZT → AZTMP → AZTDP → AZTTP; ddI → ddIMP → succinoddAMP → ddAMP → ddADP → ddATP; ddC → ddCMP → ddCDP → ddCTP; d4T → d4TMP → d4TDP → d4TTP; 3TC → 3TCMP → 3TCDP → 3TCTP; ABC → ABCMP → carbovir(CBV)MP → CBVDP → CBVTP; and (-)FTC → (-)FTCMP → (-)FTCDP → (-)FTCTP.

As a competitive inhibitor of the normal substrate, the ddNTP will inhibit incorporation of this substrate into the growing DNA chain; as an alternate substrate it will be incorporated into this chain (as ddNMP), thereby acting as a chain terminator (since ddNMP is missing the 3'-hydroxyl group required for further chain elongation). This mode of action is exemplified for AZT in Fig. 4 based on the original data of Mitsuya et al. [5] and Furman et al. [9], but is, with the necessary changes, also valid for all the ddN analogues.

3. Nucleotide reverse transcriptase inhibitors (NtRTIs)

NtRTIs should be clearly distinguished from the NRTIs as they are nucleotide analogues (not nucleoside analogues), which means that they only need two (not three) phosphorylation steps to be converted to their active form. Most importantly, they contain a phosphonate group that cannot be cleaved by hydrolases (esterases), which would make it more difficult to cleave off these compounds, once incorporated at the 3'-terminal end, compared with their regular nucleotide counterparts (i.e. AZTMP, ddAMP, ddCMP, etc.). The prototype of the NtRTIs, (*R*)-9-(2-phosphonomethoxypropyl)adenine (tenofovir) (Fig. 5), was first described in 1993 [10]. The oral prodrug form of tenofovir, tenofovir disoproxil fumarate (TDF) (Viread®), has become one of the most frequently prescribed drugs for the treatment of HIV infections (AIDS). Since 2008, it has also been approved for the treatment of chronic hepatitis B virus infections. The mode of action of tenofovir is further illustrated in Fig. 6.

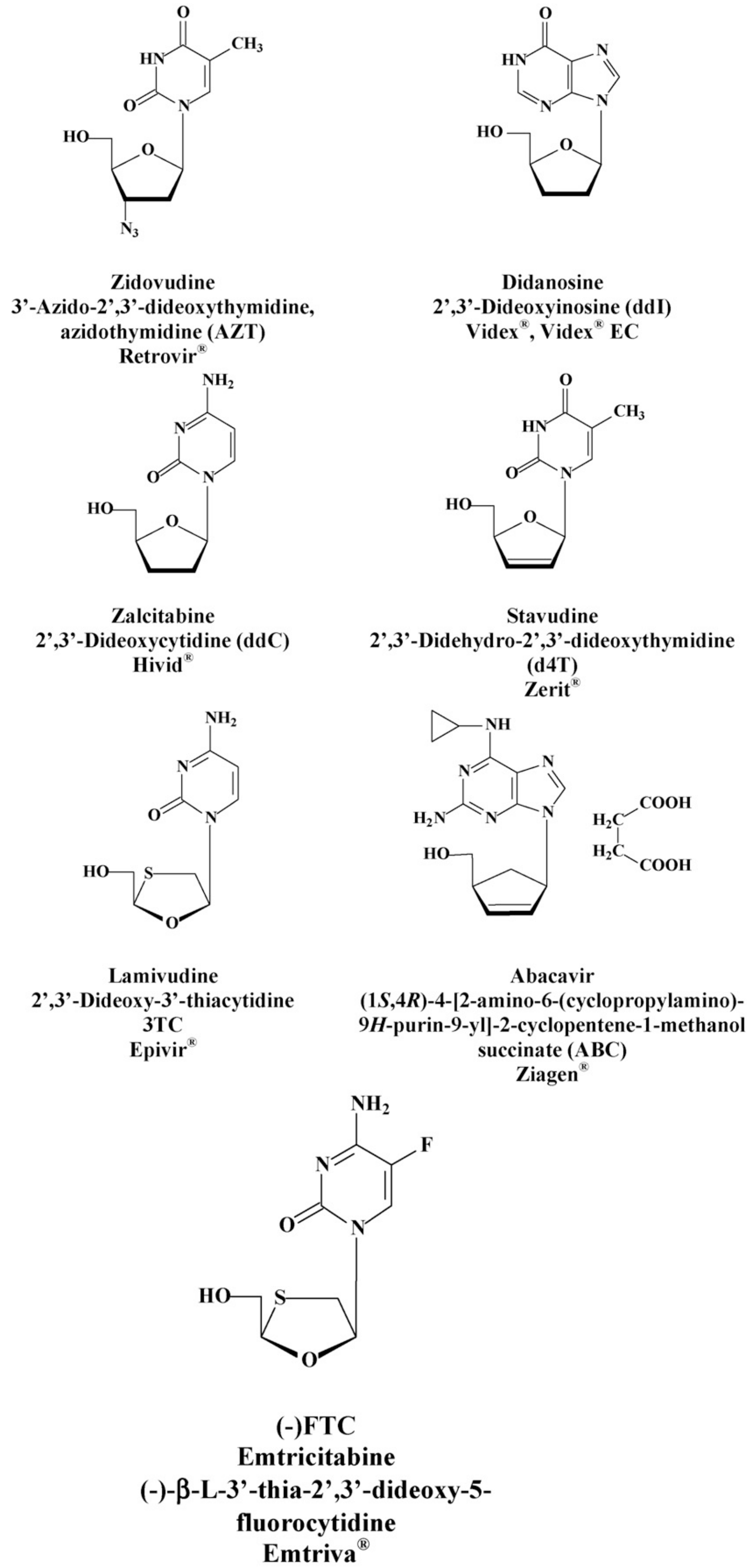


Fig. 3. Structural formulae of the nucleoside reverse transcriptase inhibitors (NRTIs) zidovudine, didanosine, zalcitabine, stavudine, lamivudine, abacavir and emtricitabine.

Table 1
Approved antiretroviral drugs in the USA and Europe.

Generic name	Brand name	Manufacturer	Date of FDA approval
Zidovudine	Retrovir	GlaxoSmithKline	19 March 1987
Didanosine	Videx (tablet)	Bristol-Myers Squibb	9 October 1991
	Videx EC (capsule)	Bristol-Myers Squibb	31 October 2000
Zalcitabine	Hivid	Hoffmann-La Roche	19 June 1992
Stavudine	Zerit	Bristol-Myers Squibb	24 June 1994
Lamivudine	Epivir	GlaxoSmithKline	17 November 1995
Saquinavir	Invirase (hard gel capsule)	Hoffmann-La Roche	6 December 1995
	Fortovase (soft gel capsule)	Hoffmann-La Roche	7 November 1997
Ritonavir	Norvir	Abbott Laboratories	1 March 1996
Indinavir	Crixivan	Merck	13 March 1996
Nevirapine	Viramune	Boehringer Ingelheim	21 June 1996
Nelfinavir	Viracept	Agouron Pharmaceuticals	14 March 1997
Delavirdine	Rescriptor	Pfizer	4 April 1997
Efavirenz	Sustiva (USA)	Bristol-Myers Squibb	17 September 1998
	Stocrin (Europe)	Merck	17 September 1998
Abacavir	Ziagen	GlaxoSmithKline	17 December 1998
Amprenavir	Agenerase	GlaxoSmithKline	15 April 1999
Lopinavir + ritonavir	Kaletra	Abbott Laboratories	15 September 2000
	Aluvia (developing world)	Abbott Laboratories	15 September 2000
Tenofovir disoproxil fumarate (TDF)	Viread	Gilead Sciences	26 October 2001
Enfuvirtide	Fuzeon	Hoffmann-La Roche & Trimeris	13 March 2003
Atazanavir	Reyataz	Bristol-Myers Squibb	20 June 2003
Emtricitabine	Emtriva	Gilead Sciences	2 July 2003
Fosamprenavir	Lexiva (USA)	GlaxoSmithKline	20 October 2003
	Telzir (Europe)	GlaxoSmithKline	20 October 2003
Tipranavir	Aptivus	Boehringer Ingelheim	22 June 2005
Darunavir	Prezista	Tibotec, Inc.	23 June 2006
Maraviroc	Celsentri (Europe)	Pfizer	18 September 2007
	Selzentry (USA)	Pfizer	18 September 2007
Raltegravir	Isentress	Merck & Co., Inc.	12 October 2007
Etravirine	Intelence	Tibotec Therapeutics	18 January 2008
Fixed dose drug combinations			
Lamivudine and zidovudine	Combivir	GlaxoSmithKline	27 September 1997
Abacavir, zidovudine and lamivudine	Trizivir	GlaxoSmithKline	14 November 2000
Abacavir and lamivudine	Epzicom (USA)	GlaxoSmithKline	2 August 2004
	Kivexa (Europe)	GlaxoSmithKline	2 August 2004
TDF and emtricitabine	Truvada	Gilead Sciences	2 August 2004
Efavirenz, emtricitabine and TDF	Atripla	Bristol-Myers Squibb & Gilead Sciences	12 July 2006

FDA, US Food and Drug Administration; TDF, tenofovir disoproxil fumarate.

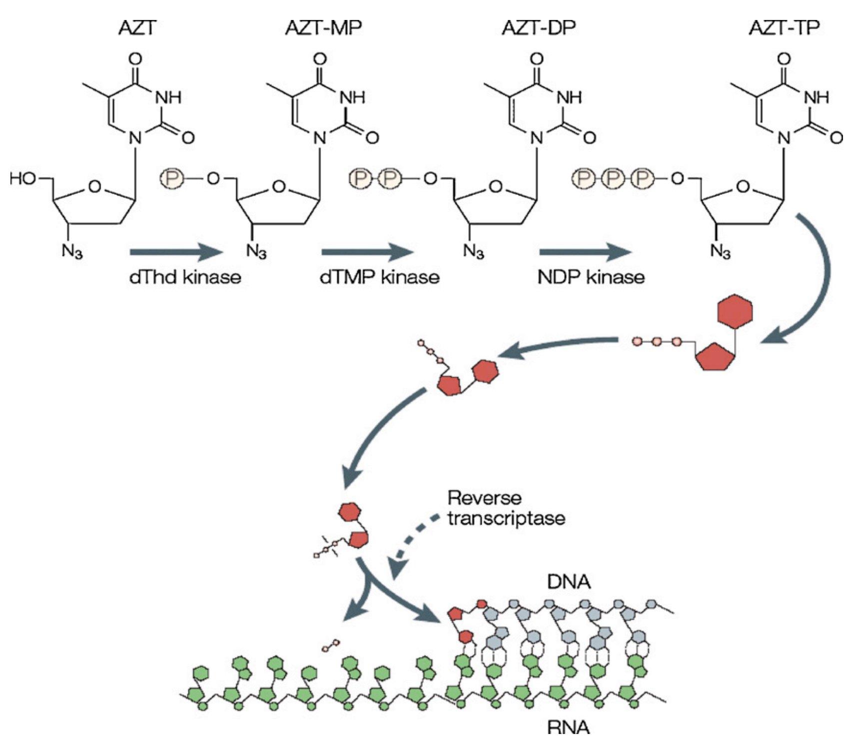


Fig. 4. Mechanism of action of zidovudine (AZT). Following phosphorylation to its triphosphate form (AZT-TP), AZT acts as a competitive inhibitor/alternative substrate with respect to dTTP in the reverse transcriptase reaction. According to De Clercq [6].

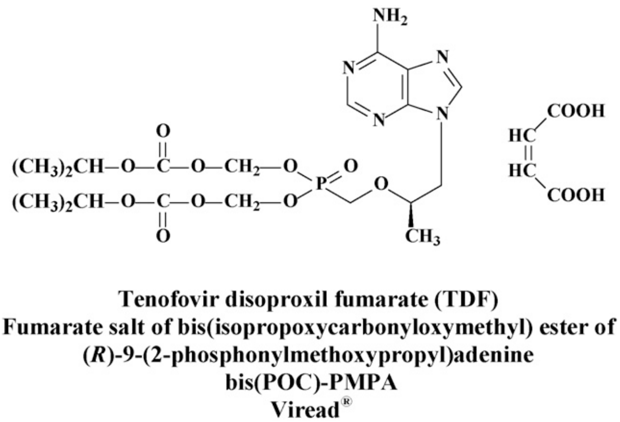


Fig. 5. Structural formula of tenofovir (PMPA) [(*R*)-9-(2-phosphonylmethoxypropyl)adenine].

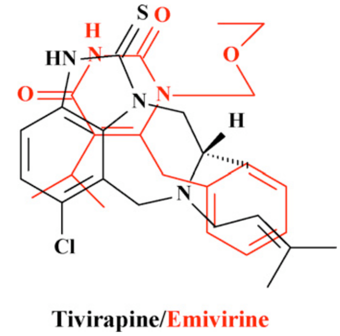


Fig. 7. Superposition of the HEPT (i.e. emivirine) and TIBO (i.e. tivirapine) analogues. According to De Clercq [14].

4. Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

The first two classes of compounds that could be categorised as NNRTIs, i.e. non-nucleoside HIV-1 RT inhibitors, were the HEPT [12] and TIBO [13] derivatives. They were the first to be

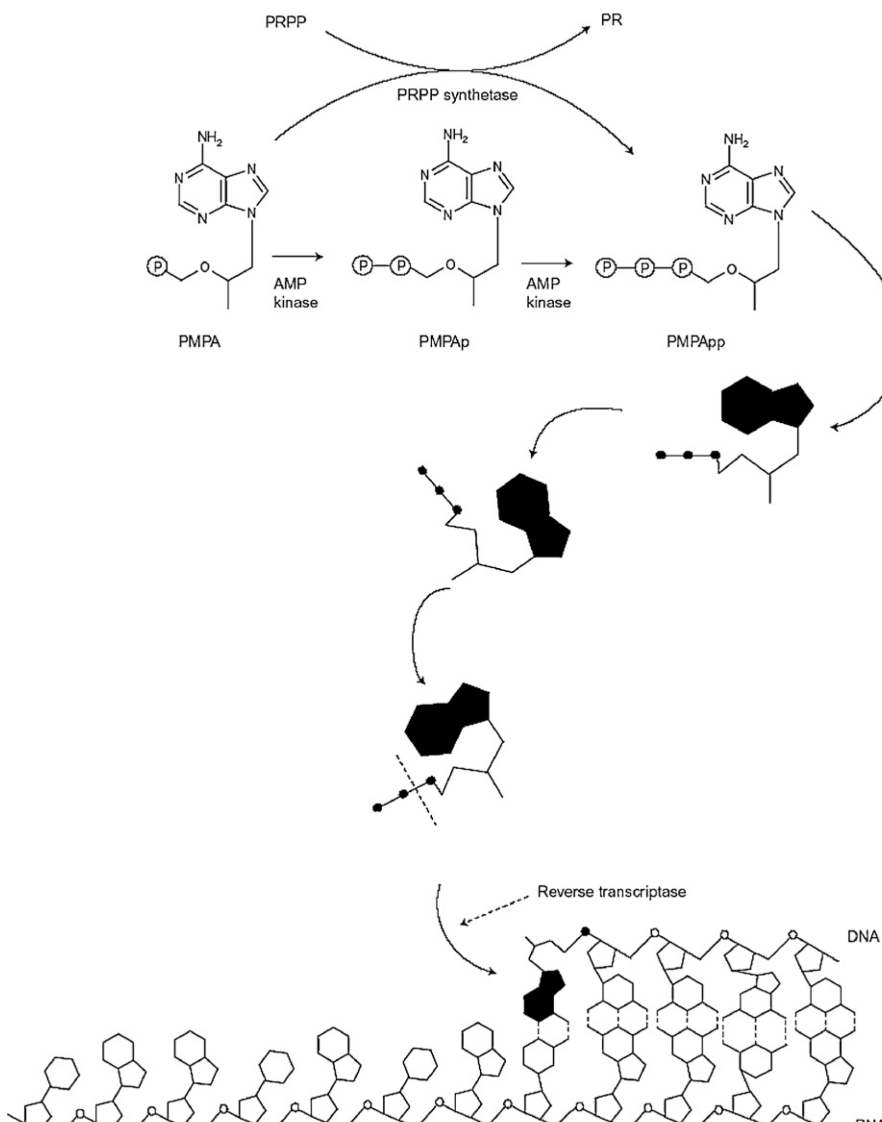


Fig. 6. Mechanism of action of tenofovir (PMPA). Following phosphorylation of tenofovir to its diphosphate, the latter acts as an obligate chain terminator in the reverse transcriptase reaction. According to De Clercq [11].

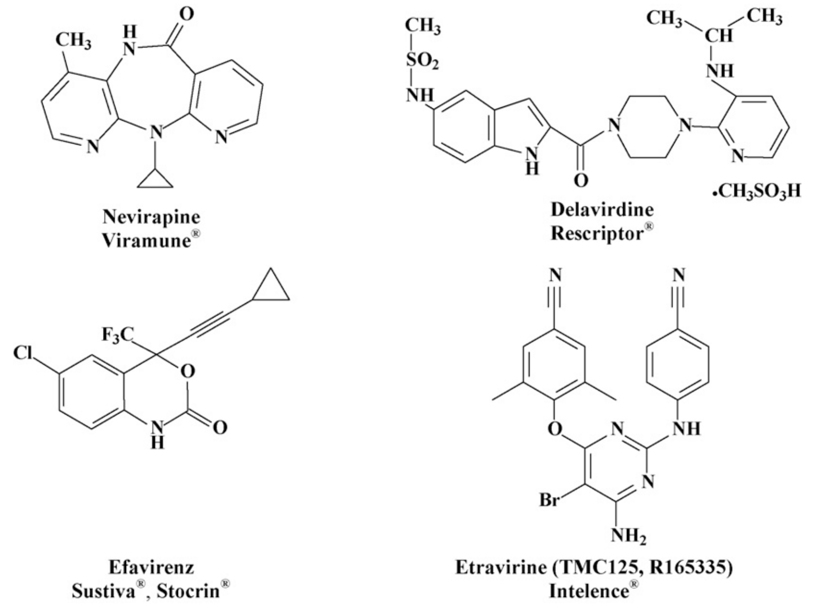
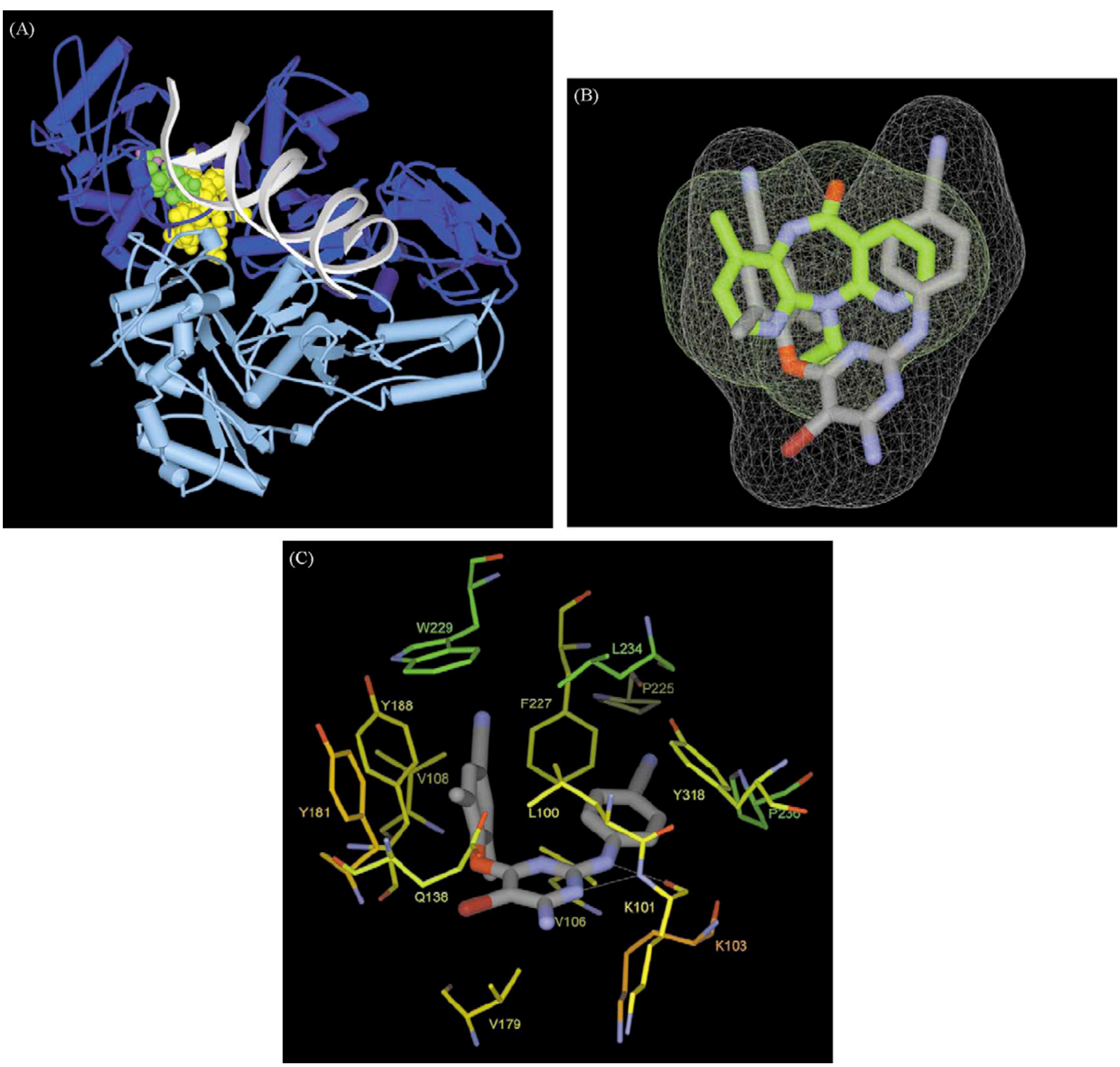


Fig. 8. Structural formulae of the non-nucleoside reverse transcriptase inhibitors (NNRTIs) nevirapine, delavirdine, efavirenz and etravirine.

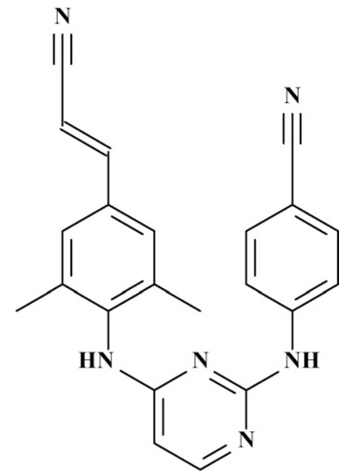


recognised as specific inhibitors of HIV-1, interacting with an allosteric (that is non-catalytic) site of the HIV-1 RT [14]. Remarkable similarities were discerned in the structural features of the HEPT and TIBO derivatives that allowed a superposition of the prototypes of these two classes of compounds, emivirine and tivirapine (Fig. 7). Although emivirine and tivirapine were themselves not further commercialised [either because their synthesis was too complicated (tivirapine) or their activity was judged not to be sufficiently potent], they paved the way for a number of NNRTIs to be effectively marketed, namely nevirapine, delavirdine, efavirenz and etravirine (Fig. 8).

Where do the NNRTIs act? They interact with a binding ('pocket') site at a close distance from the active (catalytic) site of HIV-1 RT (Fig. 9A). Superposition of the NNRTIs nevirapine and etravirine can be readily visualised (Fig. 9B). The contact points made by the NNRTI etravirine with the surrounding amino acids of the NNRTI-binding pocket are illustrated in Fig. 9C.

As the NNRTI-binding site is at a close spatial distance from the substrate (dNTP)-binding site, NNRTIs may be assumed to interfere with the active (catalytic) site, thus disturbing the normal functioning of the RT. The amino acids with which the NNRTIs interact within the NNRTI-binding pocket (Fig. 9C) may be prone to mutate, and this has proven to be the case for, among others, the amino acid residues lysine at position 103 (K103N) and tyrosine at position 181 (Y181C).

However, compared with the 'older' NNRTIs (e.g. nevirapine), the 'newer' NNRTIs etravirine and particularly rilpivirine (Fig. 10), first described by Janssen et al. in 2005 [16], retain sufficient activity against the K103N and Y181C RT mutants. Rilpivirine fulfils virtually all requirements for a successful anti-HIV drug (ease of synthesis and formulation, high potency even against HIV-1 mutants resistant to other NNRTIs, oral bioavailability and protracted duration of activity). It is expected to be approved for clinical use in 2009.



Rilpivirine
(TMC278, R278474)

Fig. 10. Structural formula of rilpivirine (TMC278, R278474).

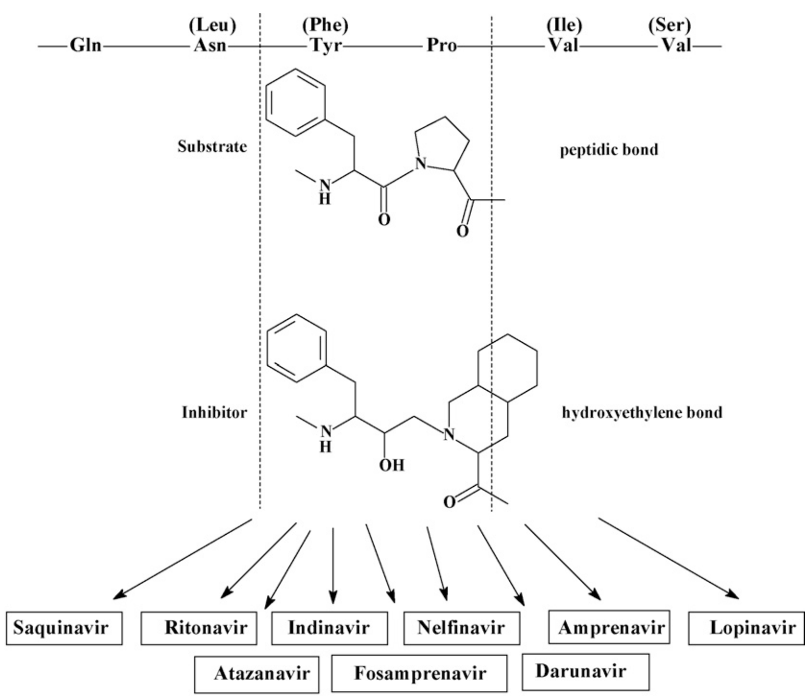


Fig. 11. Mechanism of action of protease inhibitors based on a hydroxyethylene scaffold, which mimics the normal peptide linkage cleaved by the human immunodeficiency virus (HIV) protease.

Fig. 9. (A) Human immunodeficiency virus (HIV) reverse transcriptase (RT) complexed with DNA template primer. The RT heterodimer consists of a p66 subunit (dark blue) and a p51 subunit (light blue). The two magnesium ions in the active site are shown as purple balls. The side chains of active site amino acids Tyr-183, Met-184, Asp-185, Asp-186 and Asp-10 are represented as green-coloured van der Waals spheres. Residues of the non-nucleoside reverse transcriptase inhibitor (NNRTI) binding site (Leu-100, Lys-101, Lys-103, Val-106, Val-108, Val-179, Tyr-181, Tyr-188, Pro-225, Phe-227, Trp-229, Leu-234, Pro-236 and Tyr-318) are represented as yellow-coloured van der Waals spheres. (B) Superposition of two NNRTIs, nevirapine and etravirine (TMC125). (C) Etravirine (TMC125) positioned in the NNRTI-binding site of human immunodeficiency virus type 1 (HIV-1) RT. According to Pauwels [15].

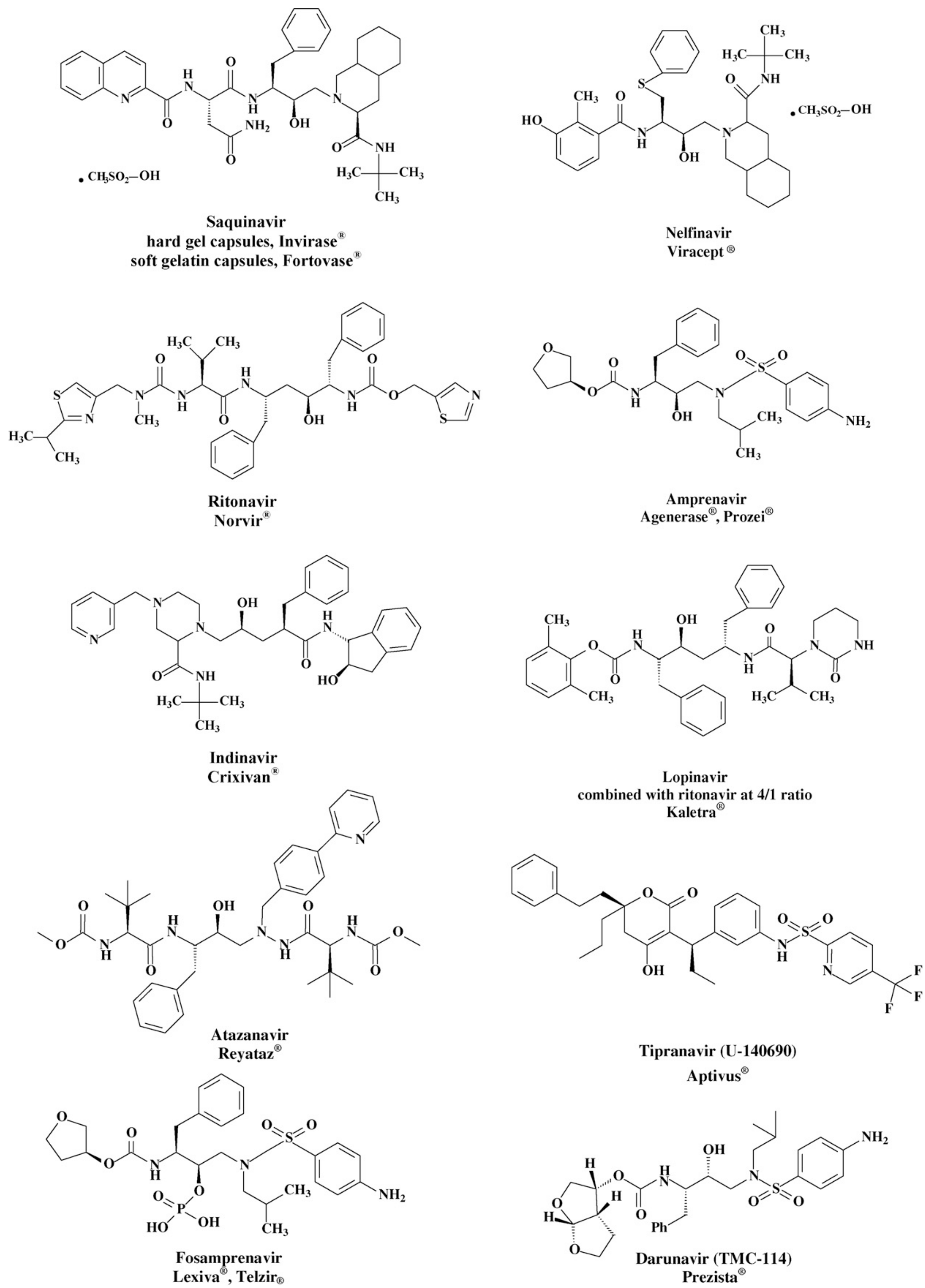


Fig. 12. Structural formulae of the protease inhibitors saquinavir, ritonavir, indinavir, nelfinavir, amprenavir, lopinavir, atazanavir, fosamprenavir, tipranavir and darunavir.

5. Protease inhibitors (PIs)

There are at present ten protease inhibitors (PIs) licensed for clinical use in the treatment of HIV infections. With the exception of tipranavir (which is based on a coumarin scaffold), all these PIs are based on the 'peptidomimetic' principle, that is they contain a hydroxyethylene scaffold which mimics the normal peptide linkage (cleaved by the HIV protease) but which itself cannot be cleaved (Fig. 11). They thus prevent the HIV protease from carrying out its normal function, that is the proteolytic processing of precursor viral proteins into mature viral proteins. The ten PIs (Fig. 12) presently available for the treatment of HIV infections are saquinavir, ritonavir, indinavir, nelfinavir, amprenavir, lopinavir, atazanavir, fosamprenavir, tipranavir and darunavir. How they fit within the active site of the HIV protease, which has a dimeric structure, is depicted in Fig. 13. Darunavir was the tenth and, so far, last PI to reach the market [18,19].

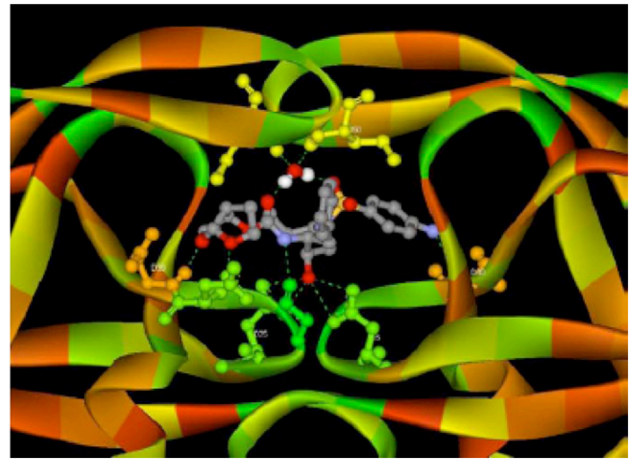


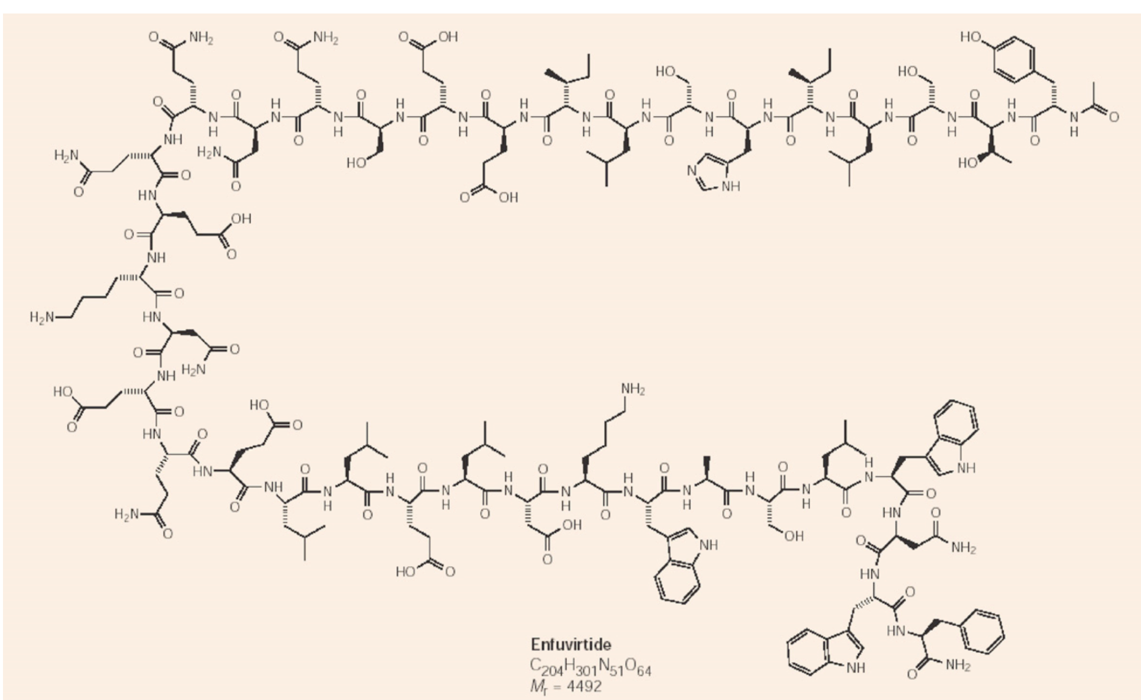
Fig. 13. Human immunodeficiency virus (HIV) protease structure with darunavir (TMC114) in the active site. According to Pauwels [17].

6. Fusion inhibitors (FIs)

There is one fusion inhibitor (FI) currently available for the treatment of HIV infections, enfuvirtide (Fig. 14), a polypeptide of 36 amino acids that is homologous to, and engages in a coil–coil interaction with, the heptad repeat (HR) regions of the viral glycoprotein gp41 [20]. As a consequence of this interaction, fusion of the virus particle with the outer cell membrane is blocked (Fig. 15). The FI enfuvirtide is the only anti-HIV compound that has a polymeric (i.e. polypeptidic) structure and hence is not orally bioavailable: it must be injected parenterally (subcutaneously) twice daily. This makes the long-term use of enfuvirtide cumbersome and problematic. Enfuvirtide is primarily used in salvage therapy as part of drug combination regimens.

7. Co-receptor inhibitors (CRIs)

Co-receptor inhibitors (CRIs) interact with the co-receptors CCR5 or CXCR4 used by, respectively, M (macrophage)-tropic and T (lymphocyte)-tropic HIV strains (now generally termed R5 and X4 strains, respectively) to enter the target cells. Within the whole viral cell entry process, interaction of the viral glycoprotein gp120



YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF

Enfuvirtide
DP-178, pentafuside, T20
Fuzeon®

Fig. 14. Detailed structure of enfuvirtide.

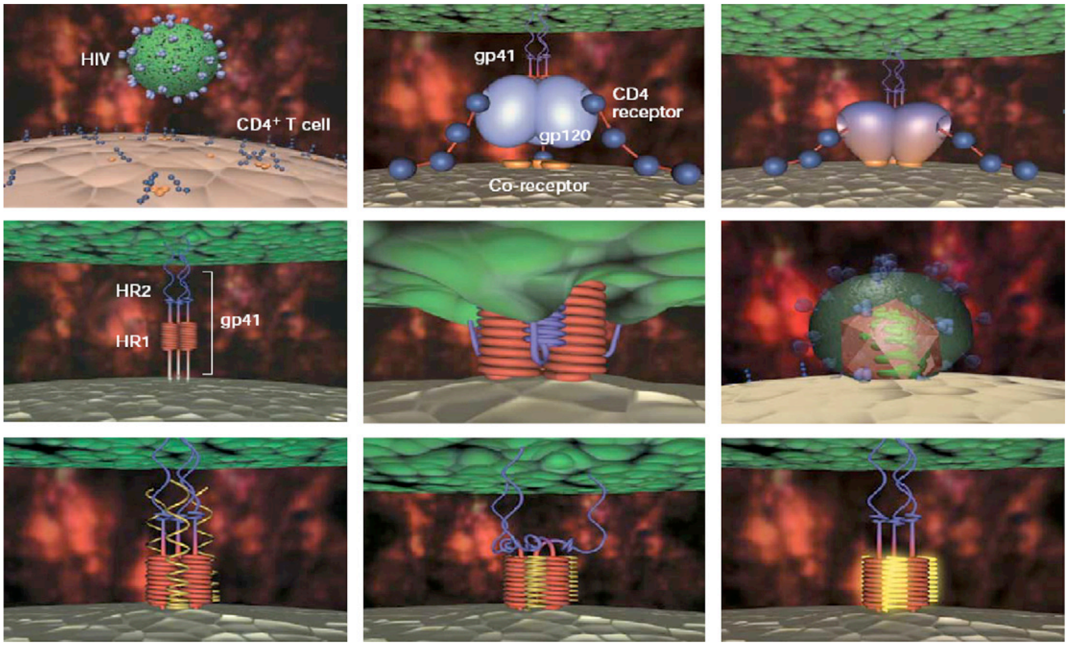


Fig. 15. Mechanism of action of enfuvirtide. Human immunodeficiency virus (HIV) enters the host cell through several separate but co-operative steps: attachment, co-receptor binding and fusion. HIV predominantly infects T-cells carrying the CD4 antigen through an initial association of the viral envelope glycoprotein gp120 with the CD4 receptor on the host cell. After this initial attachment, a conformational change is believed to occur in the viral glycoprotein gp120 that allows its further association with host cell chemokine co-receptors CCR5 and CXCR4. Subsequently, a conformational change in the second viral envelope glycoprotein gp41 allows it to insert the hydrophobic N terminus into the host cell membrane. The HR2 domain of gp41 then folds back on itself and associates with the HR1 domain; this process (known as gp41 zipping) leads to fusion of the viral and host cell membranes and infection of the cell. However, in the presence of a fusion inhibitor such as enfuvirtide (shown in yellow), an association between the fusion inhibitor and gp41 prevents the successful completion of gp41 zipping, thereby blocking infection. According to Matthews et al. [20].

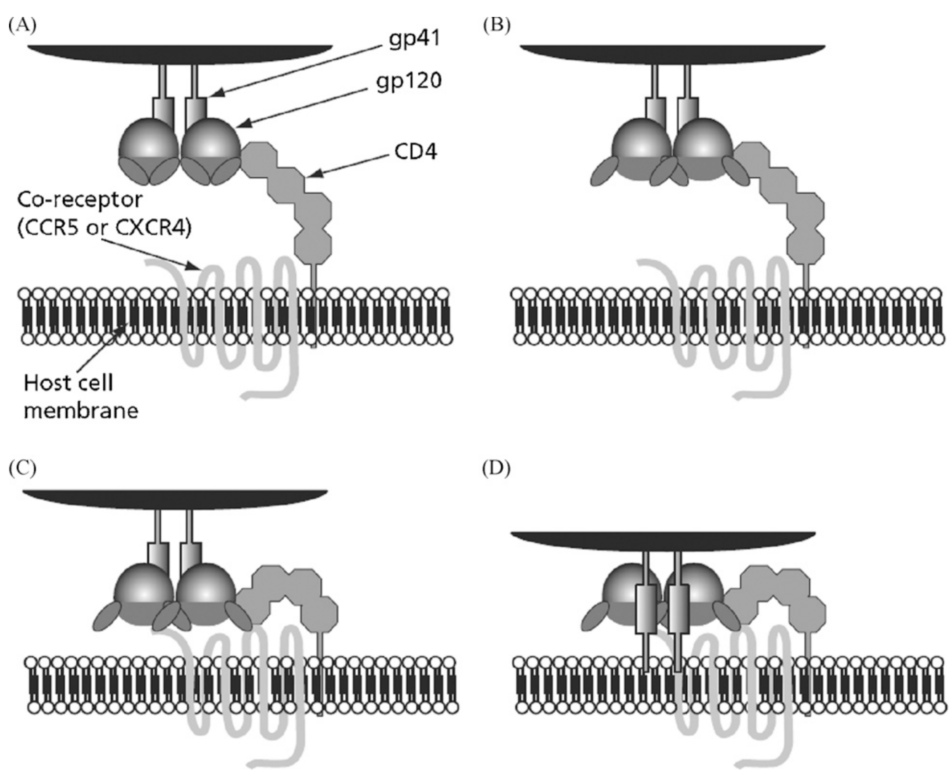
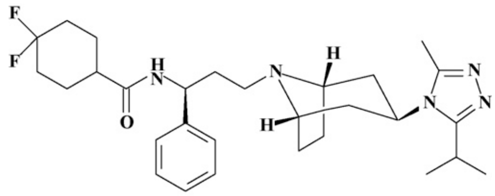


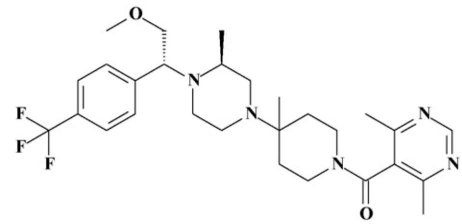
Fig. 16. Mechanism of action of co-receptor inhibitors (CRIs). Human immunodeficiency virus (HIV) glycoprotein gp120 binds to CD4 (A). This induces conformational changes in gp120 and exposure of the co-receptor binding site (B), which is a complex domain comprising the V3 loop and specific amino acid residues in C4, collectively termed the 'bridging sheet'. Exposure of the co-receptor binding site permits binding of gp120 to the co-receptor (C). Co-receptor antagonists inhibit this step by binding the co-receptor and changing its shape such that gp120 cannot recognise it. Co-receptor binding induces conformational changes in gp41 and insertion of a 'fusion peptide' into the host cell membrane (D), ultimately resulting in fusion of viral and cell membranes. Multiple gp120 co-receptor interactions are required to form a fusion pore through which the viral core can pass and infect the cell. According to Westby and van der Ryst [21].



UK-427857
Maraviroc
Selzentry®

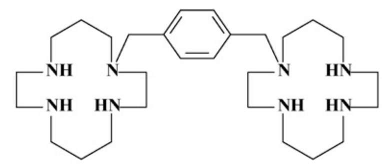
Fig. 17. Structural formula of maraviroc (UK-427857; Selzentry®).

with the co-receptor falls between the interaction of the viral glycoprotein gp120 with the CD4 receptor and fusion of the viral glycoprotein gp41 with the outer cell membrane (Fig. 16) [21]. There is, at present, only one CRI available (licensed in 2007 for clinical use), which is the CCR5 antagonist maraviroc (Fig. 17) [22]. Another, vicriviroc (Fig. 18), is forthcoming: it may be approved for clinical use in 2009. The major problem with CCR5 antagonists is that they are only active against R5 HIV strains and that from a mixed population of X4/R5 HIV strains they stimulate the selection of X4 strains. Ideally, a CCR5 antagonist should be combined with a CXCR4 antagonist so as to block both X4 and R5 HIV strains. A



SCH-D (SCH-417690)
Vicriviroc

Fig. 18. Structural formula of vicriviroc (SCH-D, SCH-417690).



JM3100
AMD3100
1,1'-[1,4-phenylene-bis(methylene)]-bis(1,4,8,11-tetra-azacyclotetradecane) octahydrochloride dihydrate
Mozobil™

Fig. 19. Structural formula of AMD3100 (Mozobil™).

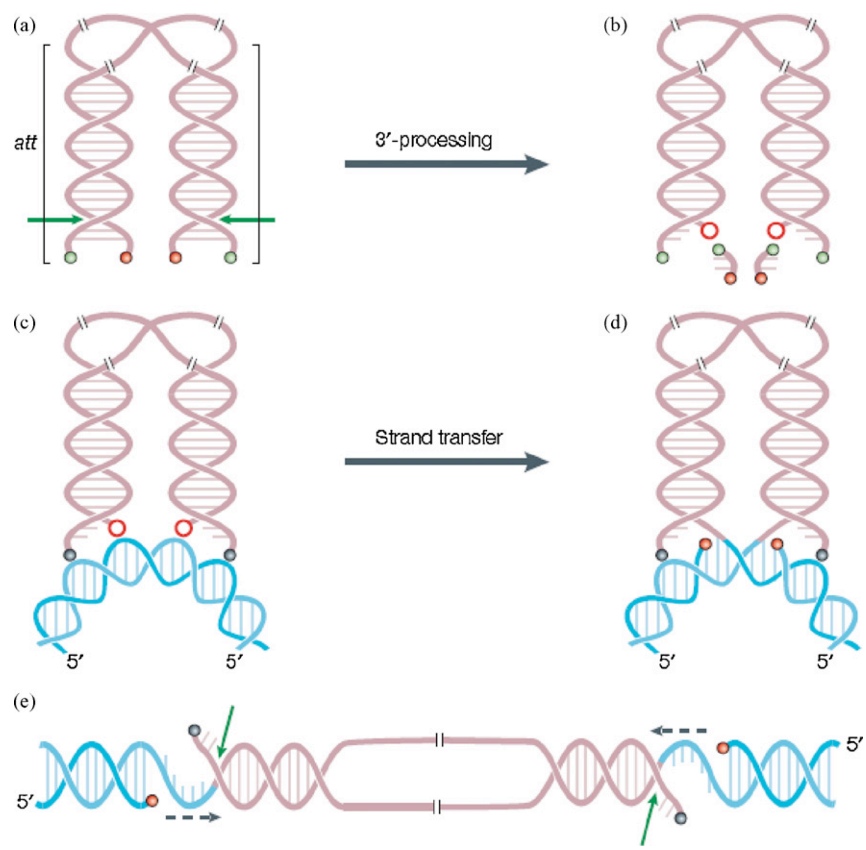


Fig. 20. The two integrase catalytic reactions (3'-processing and strand transfer). The figure shows the viral DNA recombination (*att*) sites. 3'-processing takes place in the cytoplasm following reverse transcription (Fig. 1 in [24]). It is a water-mediated endonucleolytic cleavage (green arrow in (a); Box 1, figure part a in [24]) of the viral DNA immediately 3' from the conserved CA dinucleotide (Box 1, figure part a in [24]). 3'-processing generates reactive 3'-hydroxyls at both ends of the viral DNA [red circles in (b)]; other 3'-hydroxyl ends and 5'-phosphate ends are shown as red and green dots, respectively. Integrase multimers (not shown) remain bound to the ends of the viral DNA as the pre-integration complexes (PICs) translocate to the nucleus. The second reaction (c and d) catalysed by integrase is strand transfer (3'-end joining), which inserts both viral DNA ends into a host cell chromosome (acceptor DNA in blue). Strand transfer is co-ordinated in such a way that each of the two 3'-hydroxyl viral DNA ends (red circles) attacks a DNA phosphodiester bond on each strand of the host DNA acceptor, with a 5-bp stagger across the DNA major groove (d). Strand transfer leaves a 5-base, single-stranded gap at each junction between the integrated viral DNA and the host acceptor DNA, and a 2-base flap at the 5'-ends of the viral DNA (d and e). Gap filling and release of the unpaired 5'-ends of the viral DNA (arrows in e) are carried out in co-ordination with cellular repair enzymes. According to Pommier et al. [24].

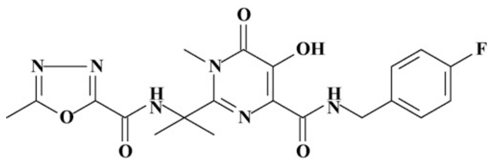


Fig. 21. Structural formula of raltegravir, the first integrase inhibitor to be licensed for clinical use.

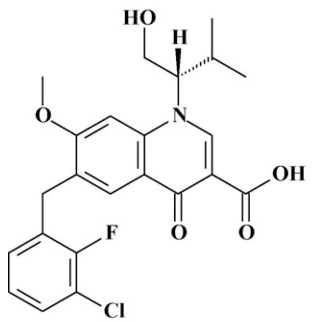


Fig. 22. Structural formula of elvitegravir.

very potent and specific CXCR4 antagonist, AMD3100 (Fig. 19), has been described [23] but this compound is not orally bioavailable. Being a CXCR4 antagonist, breaking up the interaction of CXCR4 with its normal ligand stromal-derived factor (SDF-1), it has been pursued for mobilisation upon parenteral injection of haematopoietic stem cells from the bone marrow into the blood stream from where the stem cells can then be collected for use in transplantation in patients with haematological disorders (such as non-Hodgkin's lymphoma and multiple myeloma).

8. Integrase inhibitors (INIs)

Although integrase has been pursued for many years as a potential target for the development of new anti-HIV compounds, the first integrase inhibitor (INI) licensed for clinical use, raltegravir, has only recently (in 2007) been approved. The HIV integrase has essentially two important catalytic functions (3'-processing and strand transfer) (Fig. 20). Raltegravir (Fig. 21) is targeted at the strand transfer reaction, and so is elvitegravir (Fig. 22), which is at present still in clinical (phase III) development. Elvitegravir is intended for once-daily dosing (orally), whilst raltegravir has to be administered twice daily. It has proven highly effective in reducing viral loads in HIV-infected patients [25–27].

9. Anti-HIV drug combinations: highly active antiretroviral therapy (HAART)

Since 1996, the importance of anti-HIV drug combination regimens has become widely accepted. What has been common practice for the treatment of tuberculosis (i.e. a combination of three tuberculostatics) has also been introduced for the treatment of AIDS: it was even given its own acronym, HAART, for highly active antiretroviral therapy. Combination of three (or more) anti-HIV compounds is aimed at the same goals as for the treatment of tuberculosis: (i) to obtain synergism between different compounds acting at different molecular targets; (ii) to lower the individual drug dosages to reduce their toxic side effects; and (iii) to diminish the likelihood of development of drug resistance. Of the 25 compounds that have been formally licensed for clinical use, some are not yet widely available and others (e.g. delavirdine and zalcitabine) are no longer available or prescribed, but the number of those available is still sufficiently high to allow for an astronomically high number of possible drug combinations (Fig. 23). Whilst in theory the number of possible anti-HIV drug combinations has been rapidly growing, the number of pills that have to be taken daily for all drugs combined has been drastically reduced from more than 20 pills daily in 1996 to one single daily pill in 2006. Fig. 24 depicts the evolution of the fixed-dose combinations from its early beginning (with AZT in 1987) to Atripla® in 2006 (Fig. 25). The cornerstone in the treatment of AIDS has become TDF. It is now

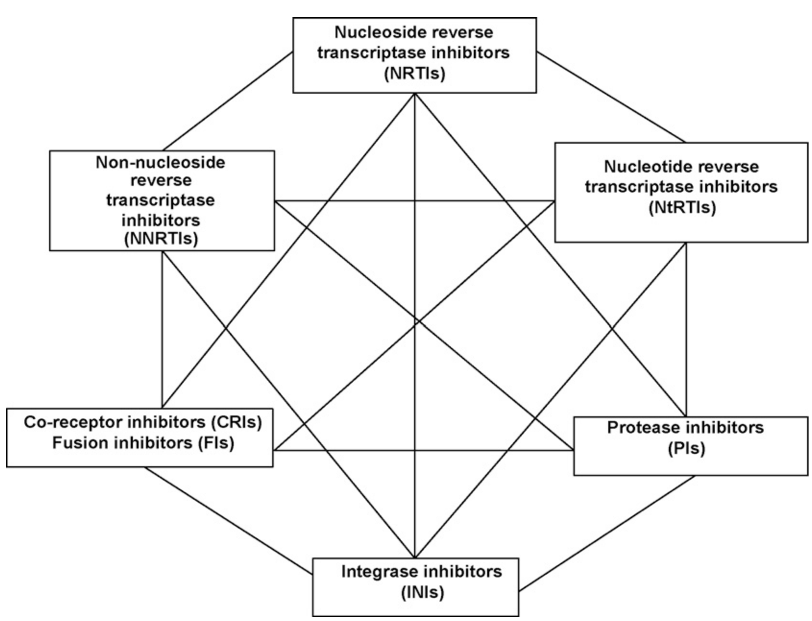


Fig. 23. Theoretically possible anti-HIV (human immunodeficiency virus) drug combinations.

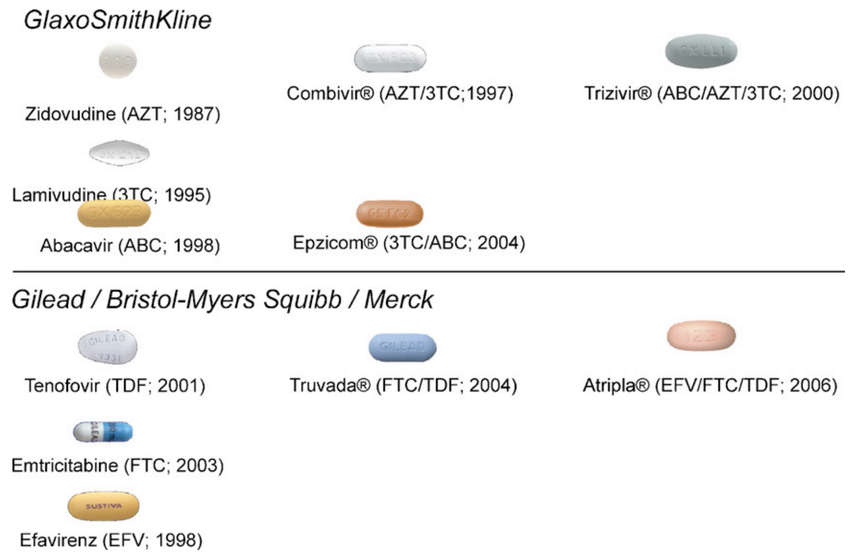


Fig. 24. Evolution of fixed-dose combinations.

Fig. 25. Anti-HIV (human immunodeficiency virus) drug combination strategy in the year 2006.

available in three formulations, including tablets containing 300 mg of TDF per tablet (Viread®), tablets of 300 mg TDF combined with 200 mg emtricitabine per tablet (Truvada®) and tablets of 300 mg TDF combined with 200 mg emtricitabine and 600 mg efavirenz per tablet (Atripla®). The latter is the only multiple-drug combination (containing a NRTI, a NtRTI and a NNRTI) that can be given as a single pill daily.

10. Conclusion

According to information from the US Centers for Disease Control and Prevention (CDC) in 2005, approximately 1 000 000–1 200 000 individuals are infected with HIV in the USA, 75% of whom (i.e. 750 000–900 000) have been diagnosed as HIV-infected. According to the Synovate Healthcare U.S. HIV Monitor Q2 2007, approximately 57% of these, that is 510 000, are on antiretroviral treatment and approximately 65% thereof (or 330 000) are on tenofovir (Atripla, Truvada or Viread), which means that tenofovir is by far the most prescribed anti-HIV drug in the USA. If the statement [28], as quoted by Hirsch [29], is correct that 'the survival benefits resulting from the use of antiretroviral drugs are estimated to have saved 3 million years of life (which compares favourably with many other interventions for chronic diseases)', tenofovir alone may be held responsible for two-thirds of the 3 million years of life saved.

Tenofovir should not only be recommended for the treatment of HIV infections but also seriously considered for the prophylaxis of HIV infections. In 2006, I wrote [30]: 'Based on (i) the original observations of Tsai et al. [31] that SIV infections in macaques can be completely prevented by tenofovir [(*R*)-PMPA], and (ii) the safety/efficacy profile that has been established for tenofovir disoproxil fumarate (TDF, Viread®) in the treatment of AIDS (HIV infection) over the past five-year period (2001–2006) since TDF was approved for clinical use, TDF could be strongly endorsed (as a single daily pill) for the pre- and post-exposure prophylaxis of HIV infections in humans.' As the original observations of Tsai et al. [31] with tenofovir for parenteral simian immunodeficiency virus (SIV) infection were later extended to intravaginal exposure [32] as well as perinatal infection [33], prophylactic use of tenofovir should be recommended to prevent HIV infection irrespective of the route by which the virus is transmitted.

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Ethical approval: Not required.

References

[1] Barré-Sinoussi F, Chermann JC, Rey F, Nugeyre MT, Chamaret S, Gruest J, et al. Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). Science 1983;220:868–71.
[2] Popovic M, Sarin PS, Robert-Gurroff M, Kalyanaraman VS, Mann D, Minowada J, et al. Isolation and transmission of human retrovirus (human T-cell leukemia virus). Science 1983;219:856–9.
[3] Mitsuya H, Popovic M, Yarchoan R, Matsushita S, Gallo RC, Broder S. Suramin protection of T cells in vitro against infectivity and cytopathic effect of HTLV-III. Science 1984;226:172–4.
[4] Broder S, Yarchoan R, Collins JM, Lane HC, Markham PD, Klecker RW, et al. Effects of suramin on HTLV-III/LAV infection presenting as Kaposi's sarcoma or AIDS-related complex: clinical pharmacology and suppression of virus replication in vivo. Lancet 1985;2:627–30.

[5] Mitsuya H, Weinhold KJ, Furman PA, St Clair MH, Lehrman SN, Gallo RC, et al. 3'-Azido-3'-deoxythymidine (BW A509U): an antiviral agent that inhibits the infectivity and cytopathic effect of human T-lymphotropic virus type III/lymphadenopathy-associated virus in vitro. Proc Natl Acad Sci U S A 1985;82:7096–100.
[6] De Clercq E. Strategies in the design of antiviral drugs. Nat Rev Drug Discov 2002;1:13–25.
[7] De Clercq E. Anti-HIV drugs. Verh K Acad Geneesk Belg 2007;64:81–104.
[8] Tantillo C, Ding J, Jacobo-Molina A, Nanni RG, Boyer PL, Hughes SH, et al. Locations of anti-AIDS drug binding sites and resistance mutations in the three-dimensional structure of HIV-1 reverse transcriptase. Implications for mechanisms of drug inhibition and resistance. J Mol Biol 1994;243:369–87.
[9] Furman PA, Fyfe JA, St Clair MH, Weinhold K, Rideout JL, Freeman GA, et al. Phosphorylation of 3'-azido-3'-deoxythymidine and selective interaction of the 5'-triphosphate with human immunodeficiency virus reverse transcriptase. Proc Natl Acad Sci U S A 1986;83:8333–7.
[10] Balzarini J, Holý A, Jindrich J, Naesens L, Snoeck R, Schols D, et al. Differential antiherpesvirus and antiretrovirus effects of the (S) and (R) enantiomers of acyclic nucleoside phosphonates: potent and selective in vitro and in vivo antiretrovirus activities of (R)-9-(2-phosphonomethoxypropyl)-2,6-diaminopurine. Antimicrob Agents Chemother 1993;37:332–8.
[11] De Clercq E. Potential of acyclic nucleoside phosphonates in the treatment of DNA virus and retrovirus infections. Expert Rev Anti Infect Ther 2003;1:21–43.
[12] Baba M, Tanaka H, De Clercq E, Pauwels R, Balzarini J, Schols D, et al. Highly specific inhibition of human immunodeficiency virus type 1 by a novel 6-substituted acyclouridine derivative. Biochem Biophys Res Commun 1989;165:1375–81.
[13] Pauwels R, Andries K, Desmyter J, Schols D, Kukla MJ, Breslin HJ, et al. Potent and selective inhibition of HIV-1 replication in vitro by a novel series of TIBO derivatives. Nature 1990;343:470–4.
[14] De Clercq E. Non-nucleoside reverse transcriptase inhibitors (NNRTIs): past, present, and future. Chem Biodivers 2004;1:44–64.
[15] Pauwels R. New non-nucleoside reverse transcriptase inhibitors (NNRTIs) in development for the treatment of HIV infections. Curr Opin Pharmacol 2004;4:437–46.
[16] Janssen PAJ, Lewi PJ, Arnold E, Daeyaert F, de Jonge M, Heeres J, et al. In search of a novel anti-HIV drug: multidisciplinary coordination in the discovery of 4-[[4-[[4-[(1E)-2-cyanoethenyl]-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile (R278474, rilpivirine). J Med Chem 2005;48:1901–9.
[17] Pauwels R. Aspects of successful drug discovery and development. Antiviral Res 2006;71:77–89.
[18] Madruga JV, Cahn P, Grinsztejn B, Haubrich R, Lalezari J, Mills A, et al. Efficacy and safety of TMC125 (etravirine) in treatment-experienced HIV-1-infected patients in DUET-1: 24-week results from a randomised, double-blind, placebo-controlled trial. Lancet 2007;370:29–38.
[19] Lazzarin A, Campbell T, Clotet B, Johnson M, Katlama C, Moll A, et al. Efficacy and safety of TMC125 (etravirine) in treatment-experienced HIV-1-infected patients in DUET-2: 24-week results from a randomised, double-blind, placebo-controlled trial. Lancet 2007;370:39–48.
[20] Matthews T, Salgo M, Greenberg M, Chung J, DeMasi R, Bolognesi D. Enfuvirtide: the first therapy to inhibit the entry of HIV-1 into host CD4 lymphocytes. Nat Rev Drug Discov 2004;3:215–25.
[21] Westby M, van der Ryst E. CCR5 antagonists: host-targeted antivirals for the treatment of HIV infection. Antivir Chem Chemother 2005;16:339–54.
[22] Perros M. CCR5 antagonists for the treatment of HIV infection and AIDS. Adv Antiviral Drug Design 2007;5:185–212.
[23] De Clercq E. The bicyclam AMD3100 story. Nat Rev Drug Discov 2003;2:581–7.
[24] Pommier Y, Johnson AA, Marchand C. Integrase inhibitors to treat HIV/AIDS. Nat Rev Drug Discov 2005;4:236–48.
[25] Grinsztejn B, Nguyen BY, Katlama C, Gatell JM, Lazzarin A, Vittecoq D, et al. Safety and efficacy of the HIV-1 integrase inhibitor raltegravir (MK-0518) in treatment-experienced patients with multidrug-resistant virus: a phase II randomised controlled trial. Lancet 2007;369:1261–9.
[26] Steigbigel RT, Cooper DA, Kumar PN, Eron JE, Schechter M, Markowitz M, et al. Raltegravir with optimized background therapy for resistant HIV-1 infection. N Engl J Med 2008;359:339–54.
[27] Cooper DA, Steigbigel RT, Gatell JM, Rockstroh JK, Katlama C, Yeni P, et al. Subgroup and resistance analyses of raltegravir for resistant HIV-1 infection. N Engl J Med 2008;359:355–65.
[28] Walensky RP, Paltiel AD, Losina E, Mercincavage LM, Schackman BR, Sax PE, et al. The survival benefits of AIDS treatment in the United States. J Infect Dis 2006;194:11–9.
[29] Hirsch MS. Entecavir surprise. N Engl J Med 2007;356:2641–3.
[30] De Clercq E. The role of tenofovir in the prevention of HIV infections. AIDS 2006;20:1990–1.
[31] Tsai CC, Follis KE, Sabo A, Beck TW, Grant RF, Bischofberger N, et al. Prevention of SIV infection in macaques by (R)-9-(2-phosphonylmethoxy-propyl)adenine. Science 1996;270:1197–9.
[32] Otten RA, Smith DK, Adams DR, Pullium JK, Jackson E, Kim CN, et al. Efficacy of postexposure prophylaxis after intravaginal exposure of pig-tailed macaques to a human-derived retrovirus (human immunodeficiency virus type 2). J Virol 2000;74:9771–5.
[33] Van Rompay KK, McChesney MB, Aguirre NL, Schmidt KA, Bischofberger N, Marthas ML. Two low doses of tenofovir protect newborn macaques against oral simian immunodeficiency virus infection. J Infect Dis 2001;184:429–38.