HIV/AIDS: Recent Advances in Antiretroviral Agents

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Abstract: Despite the considerable progress in antiretroviral therapy, the eradication of HIV-1 remains unfeasible. Therefore, novel agents are under investigation. The aim of this review is to summarize the conventional compounds, to describe the recently approved agents, and to take a comprehensive look at the clinically relevant findings of current research.

Key Words: HIV, antiretrovirals, CCR5, integrase inhibitors, maturation inhibitors.

INTRODUCTION

The Acquired Immune Deficiency Syndrome (AIDS) was first recognized in 1981 [1], and its causative agent, the Human Immunodeficiency Virus (HIV), was identified later in 1983 [2], although recent research has shown that the ancestor of the main group M of HIV-1 was circulating among humans early in the twentieth century [3]. Over the last 25 years, HIV-1 generated a novel pandemic affecting all geographical regions, but mostly Sub-Saharan Africa, and resulting in 60 million infections worldwide. HIV/AIDS remains an extremely important public health issue with an annual rate of 2.5 million new infections in 2007 and more than 5,000 deaths daily [4]. Albeit the considerable progress in our knowledge of HIV-1 pathogenesis and immunology, attempts to develop an effective and safe vaccine, which is the ideal answer to the problem, ended in failure. The great genetic variability of HIV-1, the virus capability of evading the host's immune responses, and the early creation of latent viral reservoirs pose significant difficulties and challenges to medical research [5].

The initial use of Zidovudine –an inhibitor of the reverse transcriptase (RT) of HIV-1– in AIDS therapy [6] was followed by a better understanding of the replication cycle of HIV-1 and an unprecedented development of several classes of antiviral agents. The revolutionary introduction of highly active antiretroviral treatment (HAART) –a combination of at least three drugs including either a protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI), and two nucleoside/nucleotide reverse transcriptase inhibitors (NRTI/NtRTI)– resulted in dramatically decreased morbidity, improved life expectancy [7], and cost-effective care for HIV-1 infected individuals [8]. In spite of the medical triumphs of HAART, HIV-1, unfortunately, generates rapidly reservoirs of latently infected resting $CD4^+$ T cells during primary infection with a long mean half life [9, 10], even when plasma vireamia is successfully controlled, making unachievable the ultimate therapy goal of its eradication [11]. Moreover, standard treatments fail to adequately suppress HIV-1 viral load because of the appearance of resistant viral species, side effects or lack of therapy adherence [12]. The intense pace of research led to a wide range of effective compounds and, currently, more than 20 antiretroviral drugs have been approved (Table **1**), which are grouped in 6 discrete mechanistic classes: NRTIs/NtRTIs, NNRTIs, PIs, fusion inhibitors, CCR5 antagonists, and integrase inhibitors [11]. The initiation and the selection of the appropriate therapeutic regimen remains a difficult process that should address many interdependent issues, including drug properties, patients' compliance, resistant viral isolates and adverse effects [13].

The aim of this review is to describe the replication cycle of HIV-1 and the extensively administered classes of NRTIs/NtRTIs, NNRTIs and PIs, to discuss the newly or recently approved CCR5 antagonists and integrase inhibitors, and to highlight, among the enormous literature concerning HIV-1 therapy, the major clinically relevant findings of current research.

HIV-1 REPLICATION CYCLE

Mature HIV-1 particles are spherical with a diameter of about 100-120 nanometres. Approximately 72 spikes of viral Envelope (Env) glycoproteins (gp) and some cellular proteins are embedded in a lipid bilayer of cellular origin that encases the viral core [14]. The precursor molecule gp160 is proteolytically processed by a cellular convertase in the Golgi apparatus to produce the Env glycoprotein, a heterodimer that contains the surface gp120, which is noncovalently attached to the transmembrane subunit gp41. Each spike contains three gp120 and three gp41 molecules, held together in a triangular symmetry [14-16]. The core consists of the following major structural proteins: the protein p17 attached to the inner surface of the viral membrane, the protein p24 implicated in the creation of the capsid and

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Table 1. Drugs Currently Approved by the United States Food and Drug Administration for the Treatment of HIV-1 Infection

Generic Name	Trade Name	Class	Chemical Description
Abacavir (ABC)	ZIAGEN/TRIXIVIR[1]/ EPZICOM[2]	NRTI*	(1S,4R)-4-[2-Amino-6- (cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol sulfate (salt) (1:1)
Didanosine (ddi)	VIDEX EC	NRTI	Inosine, 2',3'-dideoxy-
Emtricitabine (FTC)	EMTRIVA/ATRIPLA[3]/TRUVADA[4]	NRTI	(2R-cis)-4-Amino-5-fluoro- 1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl] -2(1H)-pyrimidinone
Lamivudine (3TC)	EPIVIR/COMBIVIR[5]/ EPZICOM/TRIXIVIR	NRTI	2(1H)-Pyrimidinone, 4-amino-1- ((2R,5S)-2-(hydroxymethyl)-1,3-oxathiolan- 5-yl)-
Stavudine (d4T)	ZERIT	NRTI	Thymidine, 2',3'-didehydro-3'-deoxy-
Tenofovir disoproxil fumarate (TDF)	VIREAD/ATRIPLA/TRUVADA	NtRTI**	Bis(hydroxymethyl) [[(R)-2(6-Amino- 9H-purin-9-yl)-1-methylethoxy] methyl]phosphonate,bis(isopropyl carbonate) (ester), fumarate (1:1)
Zidovudine (AZT, ZDV)	RETROVIR/COMBIVIR/ TRIXIVIR	NRTI	Thymidine, 3'-azido-3'-deoxy-
Delavirdine (DLV)	RESCRIPTOR	NNRTI***	Piperazine, 1-[3-[(1-methylethyl)amino)-2- pyridinyl]-2-pyridinyl]-4-[[5-[(methylsulfonyl) amino]-1H-indol-2-yl]carbonyl]-, monomethanesulfonate
Efavirenz (EFV)	SUSTIVA/ATRIPLA	NNRTI	2H-3,1-Benzoxazin-2-one, 6-chloro-4-(cyclopropylethynyl)-1,4- dihydro-4-(trifluoromethyl)-, (4S)-
Etravirine (ETR)	INTELENCE	NNRTI	Benzonitrile, 4-((6-amino-5-bromo-2- ((4-cyanophenyl)amino)-4-pyrimidinyl)oxy) -3,5-dimethyl-
Nevirapine (NVP)	VIRAMUNE	NNRTI	6H-Dipyrido(3,2-b:2',3'-e)(1,4)diazepin-6-one, 11-cyclopropyl-5,11-dihydro-4-methyl-
Raltegravir (RAL)	ISENTRESS	Integrase inhibitor	4-Pyrimidinecarboxamide, N-((4-fluorophenyl)methyl)-1,6-dihydro-5-hydroxy-1-methyl-2-(1-methyl-1- (((5-methyl-1,3,4-oxadiazol-2-yl)carbonyl) amino)ethyl)-6-oxo- monopotassium salt
Maraviroc (MVC)	SELZENTRY	CCR5 antagonist	Cyclohexanecarboxamide, 4,4-difluoro-N-((1S)-3-((3-exo)-3-(3-methyl-5-(1-methylethyl)-4H -1,2,4-triazol-4-yl)-8-azabicyclo(3.2.1) oct-8-yl)-1-phenylpropyl)-
Enfuvirtide (T20)	FUSEON	Fusion inhibitor	L-Phenylalaninamide,N-acetyl-L-tyrosyl- L-threonyl-L-seryl-L-leucyl- L-isoleucyl-L-histadyl-L-seryl- L-leucyl-L-isoleucyl-L-alpha- glutamyl-L-a-glutamyl- L-seryl-L-glutaminyl- L-asparaginyl- L-glutaminyl- L-glutaminyl-L-alpha- glutamyl-L-lysyl- L-asparaginyl-L-alpha- glutamyl-L-glutaminyl- L-alpha-glutamyl-L-leucyl- L-leucyl-L-alpha-glutamyl- L-leucyl-L-alpha- aspartyl-L-lysyl- L-tryptophyl-L-alan
Atazanavir (ATV)	REYATAZ	Protease inhibitor	2,5,6,10,13-Pentaazatetradecanedioic acid, 3,12-bis(1,1-dimethylethyl)-8-hydroxy- 4,11-dioxo-9-(phenylmethyl)-6-((4-(2- pyridinyl)phenyl)methyl)-, dimethyl ester, (3S,8S,9S,12S)-, sulfate (1:1) (salt) (atazanazir sulfate)
Darunavir (DRV)	PREZISTA	Protease inhibitor	(3R,3aS,6aR)-Hexahydrofuro(2,3-b)furan-3-yl N-((1S,2R)-1-benzyl-2-hydroxy-3- (N1-isobutylsulfanilamido)propyl)carbamate

(Table 1. Contd….)

Generic Name	Trade Name	Class	Chemical Description
Fosamprenavir (FPV)	LEXIVA	Protease inhibitor	Carbamic acid, [(1S,2R)-3-[[(4- aminophenyl)sulfonyl](2-methylpropyl)amino]-1- (phenylmethyl)-2-(phosphonooxy)propyl]-, C-[(3S)-tetrahydro-3-furanyl] ester, calcium salt
Indinavir (IDV)	CRIXIVAN	Protease inhibitor	(alphaR,gammaS,2S)-alpha-Benzyl-2-(tert-butylcarbamoyl)-gamma-hydroxy-N-[(1S,2R)-2-hydroxy-1-indanyl]-4-(3-pyridylmethyl)-1-piperazinevaleramide sulfate (1:1) (salt)
Lopinavir/ritonavir (LPV/r)	KALETRA	Protease inhibitor	2,4,7,12-Tetraazatridecan-13-oic acid, 10-hydroxy-2-methyl-5-(1-methylethyl)- 1-(2-(1-methylethyl)-4-thiazolyl)- 3,6-dioxo-8,11-bis(phenylmethyl)-, 5-thiazolylmethyl ester, (5S,8S,10S,11S)-, mixt. with (aS)-N-((1S,3S,4S)-4- (((2,6-dimethylphenoxy)acetyl)amino)- 3-hydroxy-5-phenyl-1-(phenylmethyl)pentyl)tetrahydro-a- (1-methylethyl) -2-oxo-1(2H)- pyrimidineacetamide
Nelfinavir (NFV)	VIRACEPT	Protease inhibitor	[3S-[2(2S*,3S*),3alpha,4abeta, 8abeta]]-N-(1,1-dimethylethyl)decahydro-2- [2-hydroxy-3-[(3-hydroxy-2-methylbenzoyl) amino]-4-(phenylthio)butyl]-3- isoquinoline carboxamide mono- methanesulfonate (salt)
Ritonavir (RTV)	NORVIR	Protease inhibitor	2,4,7,12-Tetraazatridecan-13-oic acid, 10-hydroxy-2-methyl-5-(1-methylethyl)-1-(2-(1- methylethyl)-4-thiazolyl)-3,6-dioxo-8,11- bis(phenylmethyl)-,5-thiazolylmethyl ester, (5S-(5R*,8R*,10R*,11R*))-
Saquinavir mesylate (SQV)	INVIRASE	Protease inhibitor	(S)-N-[(alphaS)-alpha-[(1R)-2- [(3S,4aS,8aS)-3-(tert-Butylcarbamoyl)octahydro- 2(1H)-isoquinolyl]-1 hydroxyethyl)phenethyl)- 2-quinaldamidosuccinamide mono-methanesulfonate (salt)
Tipranavir (TPV)	APTIVUS	Protease inhibitor	2-Pyridinesulfonamide, N-(3-((1R)-1-((6R)-, 6-dihydro-4-hydroxy-2-oxo- 6-(2-phenylethyl)-6-propyl-2H-pyran-3-yl) propyl)phenyl)-5-(trifluoromethyl)-

1. Trizivir is a fixed-dose tablet that contains three synthetic nucleoside analogues: abacavir sulfate, lamivudine, and zidovudine.

2. Epzicom is a fixed-dose tablet containing two nucleoside reverse transcriptase inhibitors: abacavir sulfate and lamivudine.

3. Atripla includes three antiretroviral drugs: efavirenz, emtricitabine, and tenofovir disoproxil fumarate.

4. Truvada is a fixed-dose tablet containing two synthetic nucleoside analogues: emtricitabine and tenofovir disoproxil fumarate.

5. Combivir is a fixed-dose tablet containing two synthetic nucleoside analogues: lamivudine and zidovudine.

* Nucleoside Reverse Transcriptase Inhibitor.

** Nucleotide Reverse Transcriptase Inhibitor.

*** Non-nucleoside Reverse Transcriptase Inhibitor.

the protein p7 involved in the nucleocapsid assembly [14]. Inside the core are the HIV-1 genome [two identical single stranded Ribonucleid acid (RNA) molecules], regulatory and accessory viral proteins, and three essential enzymes for HIV-1 replication named reverse transcriptase, integrase (IN) and protease (PR) [14].

HIV-1 primarily infects CD4+ T-lymphocytes and enters the cells after a cascade of interactions between the Env glycoproteins and the cell receptors (the primary receptor CD4 and a chemokine coreceptor) [17]. Chemokine receptors are members of the rhodopsin or serpentine receptor superfamily, which are G protein-coupled seven transmembrane (TM) receptors, having an acidic extracellular N-terminal domain, 7TM segments and an intracellular cytoplasmatic tail. The N-terminal domain is crucial for ligand binding, whereas the C-terminus is significant for G protein activation [18]. Although many chemokine receptors are capable of facilitating HIV-1 entry, only CCR5 and CXCR4 serve as the major coreceptors of HIV-1 *in vivo* [17]. The HIV-1 binding to the CD4 molecule causes a structural transformation of gp120 that reveals a previously hidden binding site for the coreceptors [19]. The ensuing binding of gp120 to the coreceptor induces further alterations that allow the interaction of heptad repeat (HR) 1 and HR2 domains of gp41 to create a thermostable six-helix bundle, which drives the membrane fusion and results eventually in the virus entry into the cell [20, 21].

Within the cytoplasm of the cell, the nucleocapsid is uncoated and the RNA genome is converted to a double stranded proviral Deoxyribonucleid acid (DNA) by RT [14,

22]. Subsequently, the viral DNA associates with viral and host proteins forming the pre-integration complex. This structure is imported in the nucleus in a process regulated by the viral protein R (Vpr) [23], and a linear double stranded DNA is finally incorporated into the host genome by IN [14, 24]. The integration is a multistep process that includes the removal of deoxynucleotides from each 3' termini of viral DNA and the strand transfer reaction in which the 3' ends are covalently linked to the host chromosome [24].

After integration, the viral DNA is transcribed to messenger RNA molecules (mRNA) and translated into proteins using the cell machinery. The regulatory proteins Transactivator of transcription (Tat), Regulator of virion (Rev) and Negative regulatory factor (Nef) are initially produced in small amounts [14]. Tat, once adequate levels have been achieved, influences considerably further gene expression by binding cellular activators of transcription and the Transactivation response element (TAR), which is present at the 5' end of all HIV-1 spliced and unspliced mRNAs in the nucleus or in the cytoplasm [14, 25]. Rev binds to the Rev responsive element (RRE) found in unspliced or incompletely spliced mRNAs, and assists their safe exportation to the cytoplasm (preventing splicing) permitting there their translation into important enzymatic and structural proteins of HIV-1 [14].

Pr55 (Gag) and Pr160 (Gag-Pol) polyproteins are products of the gag-pol gene. The Gag precursor yields structural proteins, whereas the procession of the Gag-Pol protein results additionally in the production of the essential enzymes RT, IN and PR [14]. The polyproteins are self-assembled at the plasma membrane, predominantly directed by interactions of the C-terminal domains of the capsid protein p24 (CA) within the Gag polyprotein, and form a core along with viral enzymes, genomic RNA and cellular components [14, 26]. The structure buds through the host membrane and an immature virion is produced. The release of the particle is stimulated by the L or Late domains identified in Gag protein and by host cell factors [27, 28]. The viral proteins Nef, gp160 and the Viral protein u (Vpu) downregulate the cell CD4 levels either by targeting mature CD4 glycoproteins at the surface as does Nef or functioning intracellularly like gp160/Vpu and, thus, inhibit the premature interference of CD4 molecules with the newly formed Env protein allowing the completion of the viral life cycle [14, 29, 30]. Following the budding, the particle undergoes a functional and morphological maturation as a consequence of the cleavage of the polypeptides by PR [26].

ENTRY INHIBITORS

A plethora of pharmaceutical approaches aims to inhibit the sequential gp120-CD4 or gp120-coreceptors interactions, and the gp41-mediated fusion of cell and viral membranes [31, 32]. Among them, a CCR5 antagonist and a fusion inhibitor have been approved for clinical use.

Natural ligands, chemokine-based compounds, peptides and other small molecules, and monoclonal antibodies can bind to human cell receptors and potentially halt viral infection [18, 32]. Research on chemokines was soon abandoned because of their short half-life, unwanted inflammatory side effects and evidence of enhancing HIV infection *in vitro*. Modified chemokine agents were subsequently used to overcome the abovementioned limitations but these derivatives were still able to induce signaling and result in inflammation [18]. Therefore, antagonists acting simply as receptor occupants were preferred.

CCR5 Antagonists

CCR5 coreceptor was a compelling therapeutic target for many reasons. First, it belongs to the G protein-coupled receptor superfamily, which is tractable to discovery of potent, small-molecule drugs. Second, CCR5-using HIV strains prevail in most transmissions. Third, Δ32 homozygotes, who carry a 32 base pairs deletion in the CCR5 coding region that results in a premature protein remaining intracellularly, exhibit remarkable resistance to HIV-1 infection without apparent consequences for the immune status or for general health [33]. TAK-779, a quaternary ammonium anilide, was a nonpeptide CCR5 antagonist with low molecular weight, adequate potency [34] and a binding site within the transmembrane helices of CCR5 [35]. However, it was not further developed due to its variable activity against HIV-1 and its poor oral bioavailability [18]. Aplaviroc, a spiroketopiperazine based compound, showed antiviral activity in laboratory experiments, had potential for oral administration, and performed well in clinical investigations. However, the occurrence of severe hepatotoxicity terminated its development [18, 36]. Maraviroc is a specific, slowly reversible, noncompetitive, small molecule, which binds to a pocket formed by the transmembrane domain of CCR5 and impedes the HIV-1 gp120-CCR5 interaction [33, 37-40]. It was positioned as the first drug targeting a host protein rather than a viral enzyme that received approval by the United States Food and Drug Administration (FDA), and is indicated for use - after the performance of a coreceptor tropism assay - as part of a multidrug cocktail in adult treatment-experienced patients with CCR5-tropic multi-drug resistant strains [11, 33]. Virologic failure to Maraviroc is often related to the outgrowth of preexisted CXCR4-tropic viral population that remained undetected by tropism assays at study entry or with tropism switches occurring over time [37, 41, 42]. Although amino acid substitutions in the V3 loop of gp120 have been described in patients harboring CCR5-tropic strains at failure of Maraviroc-containing regimens [41], the resistance profile of Maraviroc is not yet fully characterized [42].

Many other experimental CCR5-related agents are being evaluated and will be probably added to the growing set of antiretroviral therapeutics. SCH-C, an oxime piperidine compound, was one of the first promising CCR5 inhibitors to be described. However, a moderate but dose-dependent prolongation of the corrected cardiac QT interval in test participants, attributed probably to a modest affinity of SCH-C for a potassium ion channel associated with myocardial repolarization, led researchers to pursue SCH-C derivatives [43]. Among a series of piperizine core compounds, Vicriviroc ($C_{28}H_{38}F_3N_5O_2$), with a 2 to 40 fold increased potency against CCR5-utilizing strains and activity against a Clade G Russian isolate, was finally deployed [18, 43]. Later on, Vicriviroc displayed sustained viral suppression in Phase II studies, and has now reached Phase III clinical trials, which will evaluate the benefit of the addition of a Vicriviroc single once-daily dose to an optimized background therapy [36]. A

molecule acting also *via* antagonism of the CCR5 coreceptor (SCH 532706) was recently tested in a Phase I study showing biological activity against HIV-1, a satisfactory safety profile and suitability for once-daily dosing [44].

Monoclonal Antibodies

Apart from small molecule antagonists, research has also focused on monoclonal antibodies (Mab) directed against CCR5 coreceptor. PRO 140 is a promising humanized Mab and was designated a fast track product by FDA [45, 46]. It binds a complex extracellular epitope on CCR5 and hinders HIV-1 entry without affecting the natural activity of CCR5 [32]. PRO 140 probably acts as a competitive inhibitor [45]. Interestingly, in Phase I studies, PRO 140 coated CCR5 lymphocytes for more than 60 days at a dose of 5 milligrams/kilogram indicating the potential for prolonged therapeutical activity [45]. Furthermore, PRO 140 has demonstrated high-level antiviral synergy with small molecule antagonists such as Maraviroc or Vicriviroc, a finding that supports a strategy of coadministration in the future [47]. Intravenously infused PRO 140 was well tolerated in safety investigations [45] and has now reached Phase II studies [48].

CD4 receptor is also a target for Mabs-based anti-HIV-1 therapy. TNX-355 (also known as Ibalizumab) is an intravenous, humanized, nonimmunosuppressive IgG4 monoclonal antibody binding to a unique epitope on domain 2 of the CD4 molecule and is being evaluated in Phase II studies [49, 50]. TNX-355 demonstrated an acceptable safety profile in Phase I investigations [50] and synergistic activity with Enfuvirtide, an agent acting at a distal step in the entry process [51].

CXCR4 Antagonists

As CXCR4 strains are more pathogenic, the CXCR4 antagonists have also garnered scientific attention. AMD3100 was an investigational CXCR4 inhibitor with sufficient antiviral activity. However, the lack of oral bioavailability stopped its further development. AMD070 (also known as AMD11070) is an orally administered derivative of AMD3100 and is under research in Phase II studies [52]. A Phase I clinical testing in healthy male volunteers revealed that AMD070 was well tolerated without important adverse events [53].

Fusion Inhibitors

A few years ago, FDA approved another entry inhibitor, Enfuvirtide (T-20), which interferes with the fusion of cell and viral membranes [54]. Following the gp120-receptor interaction, gp41 is rearranged, exposing a previously hidden fusion peptide that is believed to penetrate the target cell membrane. Afterwards, interactions between the HR1 and HR2 domains reposition the fusion peptide and the transmembrane domain of each gp41 subunit close together permitting the formation of a fusion pore [55]. T-20 is a 36 amino acid synthetic C-peptide based on the sequence of the HR2 region that binds to HR1 domain of gp41, preventing the fusion process [32, 55]. T-20 has shown potent antiviral activity and a favorable safety profile [54]. However, the size of the peptide makes unfeasible the oral route of administration [32].

HIV-1 strains with decreased susceptibility to Enfuvirtide have been selected *in vitro* or recovered from patients treated with Enfuvirtide. Most mutations were observed in the HR1 domain of the gp41 envelope gene [42, 55]. Genotypic alterations in other regions might also affect Enfuvirtide sensitivity acting, however, indirectly without influencing the drug binding site [42, 56, 57]. Recently, the S138A substitution in the HR2 domain exhibited its potential to contribute to Enfuvirtide resistance since it was observed in 6 of 17 Enfuvirtide-experienced patients with virologic failure [58].

REVERSE TRANSCIPTASE INHIBITORS

Nucleoside and nucleotide analogues are among the most potent antiretrovirals and are considered for first-line anti-HIV-1 treatment. NRTIs/NtRTIs are targeted at the reverse transcriptase of HIV-1 blocking its enzymatic function and, thereby, inhibiting the formation of the double stranded viral DNA. NRTIs/NtRTIs exhibit advantageous features compared to other antiretroviral agents such as long intracellular half-life, continuous antiviral response despite missed doses, low protein binding and the ease of chemical manufacture [59].

NRTIs/NtRTIs are structural analogues of the naturally occurring building blocks of DNA. They act as competitors of the 2′-deoxynucleoside 5′-triphosphates (dNTP) - near the active site of HIV-1 reverse transcriptase - for the incorporation by RT in the elongating DNA chain [59]. NRTIs convert in their pharmacologically active form through a three-step phosphorylation process undertaken by cellular kinases, while NtRTIs require only two additions of phosphates to become activated. Following intracellular phosphorylation and, after removal of the diphosphate group, NRTI/NtRTIs are inserted in the strand of the newly synthesized DNA. Due to the lack of a 3'-hydroxyl (3'OH) group on the deoxyribose moiety, they act as chain terminators preventing the formation of phospodiester linkages and interrupting the addition of further nucleotides [32, 59, 60].

NRTIs/NtRTIs

The current approved armamentarium of NRTIs/NtRTIs, which are the backbone of modern HAART therapies, contains 7 compounds: Abacavir, Emtricitabine, Didanosine, Lamivudine, Stavudine, Zidovudine and Tenofovir disoproxil fumarate [11, 60]. Current nucleoside analogues, however, face the problem of resistant strains because of mutations in the gene encoding RT and, in some cases, they are responsible for long-term toxicity [59]. The RT mutations can be separated in two groups: The first category (thymidine analogue mutations-TAM) causes an increase in the rate of RT-catalyzed phosphorolysis and leads in high-level resistance to Zidovudine, while the second enhances the discrimination between deoxynucleoside triphosphate substrates and NRTI inhibitors by the binding site of RT [61]. The M184V is a highly frequent mutation belonging to the latter group and is associated with resistance to Lamivudine [62]. In spite of the difficulties, the nucleoside chemistry is expanding and many new compounds presented below are currently under evaluation. Racivir [RCV or (+)/(-)FTC] is an oxothiolane NRTI (2',3'-Dideoxy-5-fluoro-3'-thiacytidine), a 50:50 racemic mixture of the (-)- and (+)-

beta-enantiomers of Emtricitabine [63], which has performed well in terms of both safety and tolerability when administered to HIV-1 infected male volunteers [64]. In a Phase II, randomized, double-blinded, placebo-controlled trial, Racivir, replacing Lamivudine in existing regimens, reduced HIV-1 viral load in patients carrying the M184V mutation, which is usually identified in case of first-line therapy failure. Therefore, Racivir, if approved, may be considered in a combination second-line regimen [63]. Apricitabine (previously named AVX754 or SPD754) is a new deoxycytidine analogue [2(1H)-Pyrimidinone], a negative enantiomer of a failed investigational racemic mixture NRTI chemically described as 2′-deoxy-3′-oxa-4′-thiocytidine (BCH-10652) [65, 66]. Accumulated evidence has shown the antiviral potency of Apricitabine along with good tolerability, slower pace of resistance development, activity against Zidovudine- and Lamivudine- resistant strains, and ability to maintain a considerable proportion of its activity against HIV-1 viruses harbouring multiple TAM [65-69]. Another two compounds, Elvucitabine [2(1H)-Pyrimidinone, 4-amino-1-((2S,5R)-2,5-dihydro-5-], an L-cytosine nucleoside analogue of Stavudine [70], and Fosalvudine (also known as HDP 99.0003), a NtRTI developed from the previously explored 3'-fluorothymidine, are also assessed at clinical level [71].

Quite interesting is research on agents that present probably new modes of action within the NRTIs/NtRTIs class. Although the antiviral activity of NRTIs/NtRTIs is attributed to the lack of the 3'OH group, on the other hand, this particular feature decreases the affinity of NRTIs/NtRTIs for RT - compared to the analogous dNTP - and reduces the conversion rate to the active intracellular metabolite. The 4'-E-2FdA (4'-ethynyl, 2-fluorodeoxyadenosine) is a novel compound that retains the 3'OH group and has substitutions at the 4' and 2 positions of the deoxyribose sugar and of the base respectively. Nevertheless, it is capable of terminating the growing DNA chain [44]. Since the proposed mechanism of action refers to the difficulty of the primer 3'-terminus to translocate following incorporation of the compound, the 4'-E-2FdA is called Translocation-Deficient Reverse Transcriptase Inhibitor (TDRTI) [44]. Another interesting agent is KP-1212 (5-aza-5,6,-dihydro-2′-deoxycytidine), the active moiety of the oral prodrug KP-1461, which, unlike other NRTIs/NtRTIs, is not a chain terminator. Instead, it has a slightly modified base (cytosine ring) rather than a modified sugar moiety that permits multiple base pairing [72, 73]. KP-1212 acts through a novel approach - proposed some years ago - the lethal mutagenesis [74]. HIV replicates its genome and mutates at high rates producing virions with considerable genetic variation and exceptional adaptability capable of evading the host response and various therapeutic strategies. However, an elevated accumulation of mutations can impair the fitness of the viral particles [74]. Therefore, a mutagenic nucleic acid precursor, such as KP-1212, might drive, without side effects on human cells, the intrinsically high mutation rate (probably quite close to the critical threshold) of HIV to a point that the viral population is so overwhelmed with defective genomes that can not maintain itself. More specifically, KP-1212 is converted to the active form by cellular kinases and, subsequently, inserts into nascent viral DNA by RT. KP-1212 in the C or cytidine form (amino-isomer) normally allows base-pairs with guanosine, but, it can tautomerize to a T or thymidine form (imino-isomer) making base-pair with adenosine. Therefore, incorporation of KP-1212 induces transition mutations, mostly G to A and A to G substitutions, and with subsequent replication cycles, engenders C to T and T to C changes. Continual mutations exceed the natural HIV error rate. Consequently, viruses with genetic diversity beyond the bounds of viability are produced and, eventually, collapse [72, 73, 75]. The use of KP-1461/1212 has showed favourable outcomes, it was not associated with the appearance of resistant strains or cross-resistance phenomena, and probably lacks mitochondrial toxicity, an unwanted effect often seen as lactic acidosis in other NRTIs owing to the shutdown of the electron transport chain [72, 75].

NNRTIs

NNRTIs have the same target (RT) as NRTIs but the mechanism of action is different. Instead of acting as false nucleosides, they bind directly to a specific allosteric hydrophobic pocket, which is non-substrate binding site of RT, found only in the group M of HIV-1 [32, 60, 76].

Totally four approved compounds fall within the NNRTIs class: Delavirdine, Efavirenz, Etravirine, and Nevirapine [11, 60, 77, 78]. The easy selection of single mutations that alone can lead to large reduction of drug susceptibility and the development of cross resistance across the class with escalating transmission of these mutant viruses to newly infected individuals hinder the use of NNRTIs, despite their considerable potency and the low pill burden [79, 80]. The next generation NNRTI Etravirine (also known as TMC125), a diarylpyrimidine derivative, achieved approval recently and was designed to fit the pocket of HIV-1 reverse trancriptase in multiple conformationally discrete modes, even when the morphology of the pocket alters due to mutations, presenting, thus, a more robust resistance profile [76, 78]. *In vitro*, Etravirine displayed high barrier to resistance, considerable potency against many HIV-1 group M subtypes and preserved activity against resistant strains that encode L100I, K103N, Y181C, Y188L, and G190A/S mutations [78, 81, 82]. It is indicated as part of a combination regimen along with at least another two antiretroviral drugs in the therapy of treatment-experienced adults with HIV-1 infection and resistant strains to NNRTIs [78, 83]. Research on NNRTIs continues and new second-generation agents (Rilpivirine, IDX899, RDEA806, RDEA427, and RDEA640) have appeared. Rilpivirine (or TMC278), a diarylpyrimidine derivative {Benzonitrile, 4-([4-([4-([1E]-2-cyanoethenyl)-2,6-dimethylphenyl]amino)-2-pryimidinyl]amino)-}, is an encouraging candidate drug with anti-HIV activity, favorable pharmacokinetics, mild adverse effects and high barrier to resistance attributed, probably, to its ability, like Etravirine, to connect with the binding site of RT in many different ways and to its adjustment in case of RT mutations [84-86]. IDX899, might be administered once daily and seemed to have higher barrier to resistance compared to Efavirenz, while RDEA427 and RDEA640 exhibited limited cytotoxicity, activity against NNRTI-resistant strains and low potential for induction of cytochrome P450 3A4 (CYP3A4) activity [44].

Dimerization Inhibitors

Research is further oriented to dimerization inhibitors that act in a different way compared to the common interaction at the substrate-binding site. The RT is an asymmetric heterodimer consisting of two subunits, p66 and p51. The first subunit has the catalytic site and exerts both polymerase and RNaseH activities, while the latter offers structural stability. The p51 subunit lacks functionality but the dimerization of RT is needed for full enzymatic activity. The dimerization inhibitors of RT can act in three primary contact regions in the interface between the two subunits and, despite being at an early stage of development, offer opportunities for novel and promising HIV-1 drugs with higher specificity and lower probability of resistance appearance [87]. Quite recently, in addition, a new peptide has been identified that binds dimeric RT preventing, thereby, the conformational changes needed after the association of the two RT subunits (maturation step) to produce the biologically active form of the enzyme [88].

Current findings suggest that the active HIV IN is a multimer and the whole enzyme might be a homodimer. The HIV-1 protease is also a homodimeric molecule with each monomer having 99 residues. The active site of the PR is located at the bottom of a cavity in the dimer inteface. Since each monomer contributes one of the two catalytic aspartic acid residues, the disruption of the homodimeric nature of the HIV-1 PR affects considerably the catalytic activity. Therefore, apart from classical agents that will be discussed below and target the active sites of these enzymes, compounds interfering with the dimerization interfaces of the IN and PR subunits have been also designed and evaluated [44, 87].

INTEGRASE INHIBITORS

The insertion of the viral genetic material into human DNA is facilitated by integrase. This particular enzyme is comprised of three domains (N-terminal zinc finger domain, catalytic core domain, and C-terminal domain) and is involved in two steps of the integration procedure, the 3'-end processing and the strand transfer reaction [24, 32, 89]. IN has no mammalian homologues and plays a central role in HIV-1 replication. Therefore, it is an attractive molecular target for various chemotherapeutic strategies that include oligonucleotides, dinucleotides, and chemical agents, such as dicaffeoylquinic acids and 2,4-dioxobutanoic acid analogous [32].

Raltegravir potassium, the first FDA-approved inhibitor of the HIV-1 integrase strand transfer activity, ushered in a new epoch for HIV-1 therapy. It evolved from 5,6-dihydroxypyrimidine-4-carboxamides and N-methyl-4-hydroxypyrimidinone-carboxamides, which had shown an inhibitory effect on the catalytic activity of integrase [89]. The empirical formula of Raltegravir is $C_{20}H_{20}FKN_6O_5$ and the molecular weight is 482.51 [90]. Raltegravir is recommended for treatment-experienced HIV+ individuals, infected with mutants resistant to multiple drugs, and naïve to integrase inhibitors [11, 90, 91]. Raltegravir is given orally, without low-dose Ritonavir boosting to achieve therapeutic levels, and is metabolized by glucuronidation, specifically by the enzyme uridine 5'-diphosphate (UDP)-glucuronosyltransferase 1A1 [92]. Major mutations in the HIV-1 genome, which are significantly associated with resistance to Raltegravir, cause an amino acid substitution at Q148 (changed to H, K, or R), at N155 (changed to H), or, less commonly, at Y143R/H/C [42, 90]. Mutations to Q148 and N155 influence the dissociation rate of Raltegravir rather than its binding to the pre-integration complex [90]. The combination of at least two primary mutations and one or more minor amino acid substitutions contributes to Raltegravir failure [42]. Minor mutations in the Q148H/K/R pathway contain L74M + E138A, E138K and G140S. The pattern Q148H + G140S dominates in this pathway and confers the greatest loss of Raltegravir susceptibility [42].

Elvitegravir (also known as GS 9137), a low-molecular-weight modified quinolone antibiotic, chemically described as [6-(3-chloro–2-fluorobenzyl)-1-[(2S)-1hydroxy-3-methylbutan-2-yl]–7methoxy–4–oxo-1,4-dihydroquinoline-3-carboxylic acid], is another integrase blocker that offers the promise of effectiveness [93, 94]. Elvitegravir, as Raltegravir, is capable of binding a divalent metal (magnesium cations-Mg^{2+}) within the active site of IN and, thus, selectively hampers the integration process, since Mg^{2+} is needed for strand transfer reactions [93]. In contrast with Raltergravir, Elvitegravir is metabolized mostly by the cytochrome P 450 enzyme [93].

PROTEASE INHIBITORS

Protease inhibitors block the activity of protease, an enzyme deployed by HIV to transform nascent polypeptides into mature proteins. PIs appeared in clinical practice in the mid 90s and remain in force in combination regimens for treatment-naïve patients along with a dual-NRTI component [11]. Both PI- and NNRTI-based regimens attain sufficient immunological and virological response and are recommended as first-line therapy. Compared to NNRTIs, protease inhibitors have increased pill burden but they are less prone to the development of resistance [11]. However, mutations, either major or minor, appear in the protease gene. The primary group includes mutations selected first in the presence of the drug or those that affect considerably the drug susceptibility. Minor mutations emerge later without a substantial effect on the phenotype improving, probably, the replication of viruses harboring major mutations [42]. Totally, nine compounds have been approved for clinical use: 1. Saquinavir mesylate, the first approved PI, which is a structural analogue of the HIV Phe-Pro protease cleavage site, 2. Atazanavir, an azapeptide protease inhibitor, 3. Fosamprenavir, a calcium phosphate ester prodrug of Amprenavir, 4. Indinavir, a peptidomimetic PI, 5. Nelfinavir, a nonpeptidic PI, 6. Ritonavir, which prevents the metabolism of other PIs, and, thus, is commonly used in conjunction with other PIs to increase their plasma levels, 7. Lopinavir/ritonavir as a ritonavir-boosted therapy with the protease inhibitor Lopinavir, 8. Tipranavir, a nonpeptidic protease inhibitor belonging to the class of 4-hydroxy-5,6-dihydro-2-pyrone sulfonamides, and 9. Darunavir, (also known as TMC114), a nonpeptidic second-generation protease inhibitor containing 3(R),3a(S), 6a(R)-bis-tetrahyrofuranyl urethane and a sulfonamide isotere [60, 95-97].

MATURATION INHIBITORS

Bevirimat [3-*O*-(3',3'-dimethylsuccinyl)betulinic acid], a derivative of aliphatic triterpenic acid with double carboxyl groups, alternatively referred to as PA-457, DSB and YK-FH312, is the first compound in the emerging class of maturation inhibitors acting, as PIs, in the late steps of HIV-1 replication [98, 99]. More specifically, it interferes with the Gag processing pathway impairing the release of SP1 - a small spacer peptide between the capsid and nucleocapsid domains in the Gag precursor - from the C terminus of CA and, thus, inducing a defect in the conversion of the Gag cleavage intermediate p25 to mature capsid protein p24 [98–100]. Bevirimat probably does not act as competitive inhibitor but interacts specifically with the CA-SP1 domain of an oligomeric form of Gag assembled in the immature particle-like viral structure [101-103]. The lack of CA-SP1 processing results in viral particles unable to form conical cores and eventually of decreased infectivity [100]. Hepatic and intestinal glucuronidation, primarily catalyzed by uridine 5'-diphosphate glucuronosyltransferase 1A3, comprise the metabolic pathway of Bevirimat, which does not interact with cytochrome P450 liver enzyme system [98, 104]. Early clinical studies support a sufficient profile of Bevirimat in both terms of safety and efficacy although mutations encoding amino acid substitutions in the CA-SP1 site might confer HIV-1 resistance to this drug candidate [105-107].

CONCLUSIONS

With the approval and successful use of many antiretrovirals, HIV infection has turned from a lethal to a chronic disease. Apart from the above-described drugs, many other compounds such as the glycoside analogues of β-galactosylceramide (entry inhibitors) [108], carbohydrate-binding agents (entry inhibitors) [109], RNaseH inhibitors [110], HIV-1 gene expression inhibitors [111], stimulators of HIV release from latent T cells (for instance Valproic acid) [112, 113], and biological response modifiers with anti-HIV activity [Poly(I)-poly(C12U)] [114] are also being investigated and can be envisaged as further therapeutic options in the future. Gene tranfer is also a promising therapeutic approach that can decrease viral load and avoid the long term complications of HAART. Recently, the first randomized, double-blinded, placebo-controlled, phase-2 cell-delivered gene transfer clinical study was conducted and examined the effect and the safety profile of a Tat-Vpr-specific anti-HIV ribosome (OZ1) delivered in autologous CD34+ hematopoietic progenitor cells. The trial showed that OZ1-transduced CD34+ therapy was safe and, despite its modest efficacy, has a potential as an alternative therapeutic modality in the future [115].

HIV-1 creates early reservoirs and the selection pressure enforced by current treatments generates resistant strains capable of evading the antiretroviral strategies. Nowadays, no agent can efficiently inhibit HIV-1 infection or block completely the viral replication. Nevertheless, no one could imagine twenty-five years ago the successful medical endeavours that followed HIV discovery and altered significantly the prognosis of the infection. Hopefully, researchers' striving for scientific excellence and development of new technologies will open an exciting era of potent and safe agents that will give humanity a permanent solution.

ABBREVIATIONS

AIDS	=	Acquired Immune Deficiency Syndrome
HIV	=	Human Immunodeficiency Virus
RT	=	Reverse Transcriptase
HAART	=	Highly Active Antiretroviral Treatment
PI	=	Protease Inhibitor
NNRTI	=	Non-nucleoside Reverse Transcriptase Inhibitor
NRTI/NtRTI	=	Nucleoside/Nucleotide Reverse Transcriptase Inhibitor
Env	=	Envelope
gp	=	Glycoprotein
RNA	=	Ribonucleid acid
IN	=	Integrase
PR	=	Protease
TM	=	Transmembrane
HR	=	Heptad Repeat
DNA	=	Deoxyribonucleid acid
Vpr	=	Viral Protein R
mRNA	=	messenger RNA
Tat	=	Transactivator of Transcription
Rev	=	Regulator of Virion
Nef	=	Negative Regulatory Factor
TAR	=	Trans-activation Response Element
RRE	=	Rev Responsive Element
CA	=	Capsid Protein
Vpu	=	Viral Protein u
FDA	=	Food and Drug Administration
Mab	=	Monoclonal Antibody
dNTP	=	2′-deoxynucleoside 5′-triphosphate
3'OH	=	3'-hydroxyl group
TAM	=	Thymidine Analogue Mutations
TDRTI	=	Translocation-Deficient Reverse Transcriptase Inhibitor
CYP3A4	=	Cytochrome P450 3A4
UDP	=	Uridine 5'-Diphosphate
SP1	=	Spacer Peptide 1

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