ELSEVIER

New targets for HIV drug discovery

Ana C. Puhl[1], Alfredo Garzino Demo[2,3,4], Vadim A. Makarov[5] and Sean Ekins[1]

[1] Collaborations Pharmaceuticals, Inc., Main Campus Drive, Lab 3510, Raleigh, NC 27606, USA
[2] Department of Microbiology and Immunology, University of Maryland, School of Medicine, Baltimore, MD, USA
[3] Institute for Human Virology, University of Maryland, School of Medicine, Baltimore, MD, USA
[4] Department of Molecular Medicine, University of Padova, Padova, Italy
[5] Bach Institute of Biochemistry, Research Center of Biotechnology of the Russian Academy of Sciences, Leninsky Prospekt 33-2, Moscow, 119071, Russia

Recent estimates suggest close to one million people per year die globally owing to HIV-related illnesses. Therefore, there is still a need to identify new targets to develop future treatments. Many of the more recently identified targets are host-related and these might be more difficult for the virus to develop drug resistance to. In addition, there are virus-related targets (capsid and RNAse H) that have yet to be exploited clinically. Several of the newer targets also address virulence factors, virus latency or target persistence. The targets highlighted in this review could represent the next generation of viable candidates for drug discovery projects as well as continue the search for a cure for this disease.

Introduction

AIDS, caused by HIV, was first recognized as a new disease in 1981 and is still one of the most significant pathogens affecting humankind [1]. Numbers published by the WHO are particularly bleak. It has claimed >35 million lives globally, and 940 000 people died of HIV-related illnesses in 2017 alone [2]. Currently, approved HIV drugs target reverse transcriptase (RT), HIV protease and integrase (IN), the C–C motif chemokine receptor type 5 (CCR5) found on the host cells [3], as well as the process of membrane fusion. HIV can be managed, albeit with a cocktail of 2–4 antiretroviral drugs that need to be taken regularly. Side effects are a concern for these drugs that need to be taken for decades now that it is treated as a chronic disease [4]. Also, many patients develop HIV-associated neurological dysfunctions, resulting in a range of cognitive and motor function deficits [5,6]. Virus can remain in the central nervous system (CNS) and replicate, which then results in the neurological disorders. This could be caused by the inability of HIV medications to cross the blood–brain barrier (BBB) [7] and inhibit HIV in the brain, which is crucial to reverse or improve HIV-associated neurocognitive disorder [8,9]. Although it is possible to improve on known classes of drugs such as the RT inhibitors [10], these continuing liabilities of current HIV treatments suggest that it is important to find drugs that can intervene at other targets whether against host or virus. The following represents a selection of predominantly newer promising targets (Table 1) that have already been modulated by small molecules or for which crystal structures are available.

Host dependency factors TPST2, SLC35B2 and ALCAM

Because HIV relies on host proteins for entry, replication and transmission, the identification of new host dependency factors (HDFs) might result in a higher barrier to drug resistance [11] and lead to curative interventions [12,13]. Host proteins hijacked by pathogens are often used for essential cellular functions such as transcription and translation once inside the cell [14,15], whereas host factors used for pathogen entry are often dispensable for cell viability, as is the case for CCR5. A CRISPR screen conducted in a $CD4^+$ T cell leukemia line identified host factors required for productive HIV infection: TPST2, SLC35B2 and ALCAM, which were not identified in earlier genome-wide searches [16]. These highlight sulfation on the HIV co-receptor CCR5 and T cell aggregation as potential targets for therapeutic intervention. The importance of sulfated tyrosines as a contribution factor to the binding of CCR5 to macrophage inflammatory protein

Corresponding author: Ekins, S. (sean@collaborationspharma.com)

https://doi.org/10.1016/j.drudis.2019.03.013

TABLE 1

Summary of HIV targets and their potential for modulation by small molecules using references to public data sources

Target	Location	Mechanism	Small molecule inhibitor references, datasets in ChEMBL and PubChem	Representative structures
TPST2	Host	Entry	[102,103] CHEMBL3178	3AP1, 3AP2, 3AP3
SLC35B2	Host	Entry		
ALCAM	Host	Spread of HIV infection		
Gag, capsid	Virus	Entry	[22–26,104–107] CHEMBL2366504 CHEMBL3800 CHEMBL3638360 CHEMBL378	5I4T, 6ES8, 3J3Q, 3J34, 5MD7, 5MCY, 3P0A
Cyclophilin A	Host		[28] CHEMBL1949	1RMH, 1AK4, 1AWR, 1FGL, 1M9C, 5FJB, 5LUD, 5NOS, 5T9U, 6GJI, 6GJJ, 6GJL, 6GJM
Protein disulfide isomerase	Host	Entry	[31,33,34] PubChem AID: 602350	3UEM, 4EKZ, 4EL1, 4JU5
Galectin-9	Host protein	Entry	[35] CHEMBL5474	2EAK, 2EAL, 2ZHK, 2ZHN, 3NV2, 3NV3, 3NV4, 3WLU
CD4-mimics	N/A	Entry	[36,37]	
BRAF-histone deacetylase complex 80	Host	Transcription		2PUY
Protein phosphatase 1	Host	Transcription	[40] PubChem AID: 2235 PubChem AID: 2358	3E7A, 3E7B, 3EGH, 3V4Y, 4MOV, 6ALZ
RNAse H	Virus	Replication	[41–43] CHEMBL2366516 PubChem AID: 372 PubChem AID: 651 PubChem AID: 366 PubChem AID: 367	3LP3, 3QIP, 4QAG, 3IG1, 3QLH, 6ELI, 5J1E, 3K2P, 2I5J, 5UV5, 6AOC, 1HRH
LEDGF/p75	Host	Transcription	[108–110] PubChem AID: 1053136	2B4J, 3F9K, 5OYM
c-SRC protein tyrosine kinase	Host	Early stages of virus entry	[47] CHEMBL986499	4MXO, 3VRO, 1FMK, 1Y57, 1YOL, 1YOM, 2BDJ, 2H8H, 2SRC, 3VRO, 3ZMP, 3ZMQ, 4MXO
Nef	Virus	Entry	[111] PubChem AID: 463187	1AVV, 1AVZ, 1EFN, 4D8D
Tat	Virus	Transcription	[67,68] CHEMBL4011 CHEMBL4609 PubChem AID: 1117361	4OR5, 4OGR, 3MI9, 3MIA
Dendritic cell immunoreceptor	Host	Infection/ propagation	[69]	5B1W, 5B1X
mTOR pathway	Host	Transcription	[70] CHEMBL2842 CHEMBL2221341 PubChem AID: 493208 PubChem AID: 504465	
JAK pathway	Host	Cell–cell viral transmission	[72,73]	
Ku70	Host	Replication		1JEY, 1JEQ
SIRT-AMPK pathway	Host	Transcription		
Cytidine deaminases	Host	Replication	PubChem AID: 602313 PubChem AID: 651812 PubChem AID: 602310	4ROV, 4ROW, 3V4J, 3V4K, 3IQS, 6BUX
Mucosa-associated lymphoid tissue translocation 1	Host	Suppression of reactivation	[84,85] CHEMBL3632452	3V4O, 3V55, 4I1R, 3UO8, 4I1P

TABLE 1 (*Continued*)

Target	Location	Mechanism	Small molecule inhibitor references, datasets in ChEMBL and PubChem	Representative structures
Toll-like receptor 4	Host	Lower HIV replication	[92,93] CHEMBL5255 PubChem AID: 1953	3FXI
Y-box-binding protein 1	Host	Replication	PubChem AID: 434959	1H95
B23/nucleophosmin	Host	Replication	[97]	2P1B, 5EHD
Natural seminal amyloids	Host	Entry inhibitor	[100,101]	3PPD, 2L3H

Abbreviation: N/A, not applicable.

(MIP)-1α, MIP-1β and HIV-1 glycoprotein 120 (gp120)–CD4 complexes and to the ability of HIV-1 to enter cells expressing CCR5 and CD4, was described almost 20 years ago [17]. Chemokine receptor type 4 (CXCR4), another important HIV-1 coreceptor, is also sulfated [17].

Activated sulfate in the form of 3′-phosphoadenosine 5′-phosphosulfate (PAPS) is needed for all sulfation reactions in eukaryotes [18]. The adenosine PAPS transporter 1, encoded by the gene *SLC35B2*, transports the activated sulfate donor PAPS from the cytosol into the Golgi lumen [19]. The protein-tyrosine sulfotransferase 2, encoded by the gene *TPST2*, then catalyzes O-sulfation on the tyrosines of secretory and plasma membrane proteins [20]. Importantly, TPST2 sulfates the N-terminal residues on CCR5 that are known to mediate interactions with the HIV envelope gp120 and also sulfates key tyrosine residues on CXCR4 – the other major co-receptor for HIV; and these tyrosine residues on CXCR4 are known to mediate important interactions with HIV gp120. In the same CRISPR screen study, the authors also demonstrated that loss of the cell adhesion molecule ALCAM (a cell surface protein expressed on activated immune cells) prevents the spread of HIV infection and might be a host target for HIV [16].

Targeting Gag cleavage proteins, capsid and cyclophilin A

Because capsid assembly and disassembly finely regulates HIV-1 replication, it represents an emerging and attractive target [21]. HIV Gag protein cleavage into its two structural proteins, matrix (MA) and capsid (CA), can dramatically affect viral production. MA- and CA-specific inhibitors have recently been identified using a HTS of 24 000 compounds [22]. Screening based on the inhibition of capsid assembly and virtual screening for molecules binding to the capsid has successfully identified several potential small-molecule compounds [23]. Bevirimat, a plant-derived natural product, had been originally identified as a weak inhibitor of HIV-1 replication and has been tested in a Phase II clinical trial, where it caused a significant viral load reduction [24]. The mechanism of action of the previously reported capsid-targeting HIV-1 inhibitor Boehringer-Ingelheim compound 1 (C1) was described, showing that C1 acts during HIV-1 maturation to prevent assembly of a mature viral capsid. However, unlike the maturation inhibitor bevirimat, C1 did not significantly affect the kinetics or fidelity of Gag processing [25]. In another study, a series of inhibitors bound to the N-terminal domain of CA [26] showed that these inhibitors induce the formation of a pocket that overlaps with the binding site for the previously reported CA inhibitors but is expanded significantly by these new, more-potent CA inhibitors.

The host cell protein cyclophilin A (CypA) binds directly to the HIV-1 capsid and modulates capsid uncoating and viral infectivity. Interference with CypA binding inhibits HIV-1 replication in cell culture [27]. A series of thiourea compounds as HIV-1 assembly and disassembly dual inhibitors was designed and synthesized targeting HIV-1 CA protein and human CypA. The results suggested that 15 compounds could block HIV-1 replication by inhibiting the peptidylprolyl *cis-trans* isomerase (PPIase) activity of CypA to interfere with capsid disassembly and disrupting CA assembly [28]. The structure of CypA in complex with an HIV-1 capsid tubular assembly was determined at 8 Å resolution by cryoEM and revealed a novel, noncanonical, second capsid-binding site on CypA that is vital for stabilizing the viral capsid [29]. The novel interaction interface of CypA could provide a new avenue for the development of therapeutic interventions that target CypA interactions with the HIV-1 capsid [29].

Protein disulfide isomerase and galectin-9

Protein disulfide isomerase (PDI) is a 57 kDa oxidoreductase of the thioredoxin superfamily that is expressed mainly in the endoplasmic reticulum (ER) of eukaryotic cells. In the ER, it catalyzes the rearrangement of incorrect disulfide bonds through isomerase activity, thus mediating proper protein folding [30]. PDI, together with additional ER secretory proteins, can be secreted to the cell surface through a regulatory pathway. PDI-catalyzed reduction of disulfides in gp120 has been shown to be crucial for HIV-1 entry into host cells [31,32]. Several agents have been described as PDI inhibitors, although none has been used therapeutically [31,33] owing to their nonspecific activities and toxicities. The discovery of a sesquiterpenoid juniferdin and an analog showed specific inhibition of PDI reductase activity and did not inhibit the other homologs of PDI [34]. Hence, their ability to inhibit the PDI-catalyzed reduction of HIV gp120 suggests they might be promising as inhibitors of viral entry. Recently, researchers reported that a sugar-binding protein called galectin-9 traps PDI on the surface of T cells making them more susceptible to HIV infection [35]. It was demonstrated that galectin-9 enhances HIV-1 infection of T cells in a PDI-dependent manner [35].

CD4 mimics

Several groups have reported the discovery and design of small-molecule CD4 mimics targeting the Phe43 cavity of HIV-1 envelope glycoprotein gp120, as entry inhibitors [36,37]. One of these groups proposed compounds with IC_{50} values as low as 150 nM. These compounds also inhibited cell–cell fusion and cell–cell HIV-1 transmission [36].

BRAF histone deacetylase complex 80

Efficient HIV-1 transcription from HIV-1 long terminal repeat (LTR) requires host cell factors and HIV-1 Tat protein [38]. The Tat protein plays an indispensable part in HIV reactivation, and histone demethylase (LSD1) promotes Tat-mediated LTR activation. BRAF–histone-deacetylase complex 80 (BHC80) is key for LSD1-triggered LTR activation. The LSD1–BHC80 complex enhances HIV-1 transcription by decreasing histone H3 lysine 4 trimethylation at the viral promoter [39] and it might be used as a new drug target to reactivate latent HIV-1.

Protein phosphatase 1

HIV-1 transcription is regulated by host cell protein phosphatase-1, it is sensitive to the reduction of intracellular iron which affects cell-cycle-dependent kinase 2 [38] and can be modulated via small-molecule inhibitors, iron chelating compounds and curcumin analogs [40].

RNAse H

The RNase H active site of HIV-1 RT has no approved therapeutics. Recent work has described inhibitors that chelate with magnesium ions and inhibit site-specific cleavage responsible for initiating the second strand of viral DNA synthesis [41]. The development of dual inhibitors of IN/RNAse H is an attractive strategy for drug development, because they are selective targets for HIV-1 chemotherapy [42]. Recently, it was demonstrated that a pyrazolecarbothioamide derivative was able to inhibit viral replication and RNase H and RNA-dependent DNA polymerase (RDDP) RT-associated activities in the low micromolar range [43].

LEDGF/p75

Lens epithelium-derived growth factor p75 (LEDGF/p75) is an epigenetic reader, transcriptional coactivator and attractive therapeutic target involved in HIV integration. It has a role in tethering protein complexes to chromatin and is linked to multiple diseases such as HIV infection. It consists of a Pro-Trp-Trp-Pro (PWWP) domain and the integrase-binding domain (IBD), which is a target for inhibiting HIV [44].

c-SRC protein tyrosine kinase

Tyrosine kinases promote viral infection from the initial binding of viral gp120 to the T lymphocyte receptor CD4 and chemokine coreceptor CXCR4 (X4 viruses) or CCR5 (R5 viruses); however, non-receptor tyrosine kinases also have crucial roles during the early stages of the HIV-1 lifecycle in T cells [45]. The SRC tyrosine kinases become activated within minutes of HIV-1 infection on $CD4^+$ T cells [46]. c-SRC tyrosine kinase is a major regulator of HIV-1 infection, participating in multiple stages of infection post-entry. Decreasing c-SRC expression and/or activity provides a new target. Because there are already numerous kinase inhibitors, this suggests that some could be repurposed [47].

Nef

The viral protein Nef of HIV is a well-known virulence factor as well as a shuttling molecular adaptor that can affect infected and noninfected cells as well as having a key role on the chemocytokine network [48,49]. Nef can reduce cell surface expression of CD4, CD8, major histocompatability complex-I (MHC-I), CD28, CD3 (HIV-2 and most SIVs), Serine incorporator 3/5 (SERINC3/5) and/or CXCR4 to suppress antigen presentation, modulate T cell activation and promote efficient release of fully infectious virion. The reduction of the cell surface expression mediated by Nef occurs by simultaneous binding to the cytoplasmic domains of various receptors and clathrin–AP protein complexes [49,50].

Tat

The early virus-encoded gene product Tat is required for robust transcription of the integrated viral genome by RNA polymerase II (RNAP II) [51] and is an attractive target for therapeutic intervention because it is expressed early during virus replication and it has no cellular homologs. Residual viremia is thought to be a major contributor to inflammation and other HIV-associated complications, leading to neurological and cardiovascular diseases [52]. Direct inhibition of Tat blocks the feedback loop that drives exponential increase in viral transcription and the production of viral particles [53]. In resting $CD4^+$ T cells, HIV-1 is maintained in a latent state by several mechanisms, which include low levels of Tat [54] or active cellular protein kinase known as TAK (cyclin T1/P-TEFb) [55], the exclusion of cellular transcription factors from the nucleus [56,57], the presence of repressors [58,59], transcriptional interference [60] and lower levels of intracellular deoxynucleoside triphosphate (dNTP) pools [61]. Transcriptional reactivation is accompanied by changes in the local chromatin structure, which is accomplished by recruitment via Tat of chromatin remodeling factors [62,63] and histone acetyltransferases. Transcriptional silencing is a multifactorial phenomenon and the *in vivo* mechanisms of latency are still incompletely understood [64,65].

It has been suggested that blocking Tat activity might help block viral reactivation and maintain the virus in a state of prolonged silencing [53,66]. Although dependence of HIV transcription on Tat has made it an attractive drug target, no approved Tat inhibitor therapeutics are currently available in the clinic. It was demonstrated that the Tat inhibitor didehydro-cortistatin A (dCA) prevents HIV-1 reactivation from latency [67]. The authors proposed that dCA treatment combined with antiretroviral treatment (ART) opens the possibility for culminating in a sterilizing cure, because it would delay or halt viral replication, reactivation and replenishment of the latent viral reservoir. Therefore, the latent pool of cells in an infected individual would be stabilized, and death of the long-lived infected memory T cells could result in a continuous decay of this pool over time [67]. The authors demonstrated the potential of this 'block-and-lock' functional cure approach based on properties of dCA [68]. Combining dCA with ART accelerates HIV-1 suppression and prevents viral rebound after treatment interruption, even during strong cellular activation in human $CD4^+$ T cells isolated from aviremic individuals. Adding dCA to ART-suppressed mice systemically reduces viral mRNA in tissues, in the bone-marrow-liver-thymus (BLT) mouse model of HIV latency and persistence [68].

Dendritic cell immunoreceptor

The dendritic cell immunoreceptor (DCIR) is a C-type lectin receptor that is expressed on dendritic cells (DCs). DCIR acts as an attachment factor with HIV-1 and is directly involved in infection via transmission to $CD4^+$ T lymphocytes. Inhibitors that decrease HIV-1 attachment and propagation have recently been

described [69], providing a potential approach for interference with the initial propagation of HIV-1 at an early stage of the viral cycle and limiting proliferation of the virus in the later stages.

mTOR pathway

mTOR inhibitors suppress HIV transcription through the viral transactivator Tat or via Tat-independent mechanisms. mTOR inhibitors Torin1 and pp242 suppressed the reactivation of latent HIV via T cell stimulants in the Bcl-2 HIV latency primary cell model and in $CD4^+$ T cells from patients on highly active antiretroviral therapy (HAART) [70]. Thus, the control of HIV latency by mTOR signaling suggests a pathway that could have therapeutic opportunities for HIV eradication [70,71].

JAK pathway

The JAK/STAT pathway is involved in HIV persistence. It was shown that the FDA-approved JAK inhibitors tofacitinib and ruxolitinib reduced the frequency of $CD4^+$ T cells harboring integrated HIV DNA and targeted key events downstream of γ-C cytokine [interleukin (IL)-2, IL-7 and IL-15] ligation to their receptors, impacting the magnitude of the HIV reservoir in memory $CD4^+$ T cell subsets *in vitro* and *ex vivo* [72,73]. JAK inhibitors represent a therapeutic approach to prevent key events of T cell activation that regulate HIV persistence and this class of drugs has the advantage of also having been tested in clinical trials [73].

Ku70

Ku70 is a host protein that interacts with HIV integrase and can downregulate the polyubiquitination level and is required for early and late stages of the viral lifecycle. Ku70 can protect integrase from the host defense system and enable HIV-1 to hijack the host cell machinery. Interfering with Ku70 therefore disrupts HIV-1 replication [74].

SIRT/AMPK pathway

HIV-1 transcription is activated by the viral Tat protein which in turn is a substrate for the deacetylase activity of sirtuin 1 (SIRT1) [75]. Tat-mediated inhibition of the SIRT1 deacetylase and the resulting hyperactivation of nuclear factor (NF)κB function could thereby directly participate in the immune dysfunctions in infected patients [76]. AMP-activated protein kinase (AMPK) is activated by a decrease in cellular ATP levels [77,78] and changes in AMPK activity (phosphorylation) are associated with alterations in SIRT1 abundance and activity. It was also demonstrated that Tat inhibited the AMPK signaling pathway through the NAD^+/SIRT1 pathway. Both processes were involved in Tat-induced HIV-1 LTR transactivation. Hence targeting the SIRT1/AMPK pathway represents a new target for HIV intervention [79].

Cytidine deaminases

The APOBEC family of cytidine deaminases plays an important part in antiviral innate immunity. The APOBEC3 (A3) enzymes A3G and A3F are coordinately expressed in $CD4^+$ T cells and can become co-encapsidated into HIV-1 virions, primarily in the absence of the viral infectivity factor (Vif) [80]. These enzymes deaminate dC to dU in nascent minus-strand viral DNA, resulting in G-to-A hypermutation in the plus-strand DNA to inhibit the replication of HIV-1 [81]. Interestingly, the expression of APO-

TABLE 2

HIV targets and number of associated molecules from ChemDB HIV, opportunistic infection and tuberculosis therapeutics database (ChemDB; https://www.niaid.nih.gov/research/chemdb)

Target listed	Number of molecules
Alpha-glucosidase	29
Alpha-mannosidase	6
Beta-glucosidase	10
Beta-glucuronidase	8
CCR2	2
CCR3	2
CCR4	2
CCR5	401
CCR8	1
CD130	3
CD4	99
CXCR2	2
CXCR4	164
Calcineurin	2
Capsid	443
Cathepsin D	75
Cyclin-dependent kinase	4
Cyclin-dependent kinase 8	17
Cyclin-dependent kinase 9	175
Cyclophilin A	7
DC-SIGN	36
DEAD-box DDX3	72
DEAD-box DDX1	1
Dipeptidyl peptidase-4	3
Enhancer binding protein 1	13
Frameshift stimulating signal	8
Gag	7
Galactosylceramide	7
Gelatinase	33
Hck	364
Histone deacetylase 1	4
Histone deacetylase 10	3
Histone deacetylase 11	3
Histone deacetylase 2	3
Histone deacetylase 3	3
Histone deacetylase 4	3
Histone deacetylase 5	3
Histone deacetylase 6	3
Histone deacetylase 7	3
Histone deacetylase 8	3
Histone deacetylase 9	3
Integrase	16 354
Integrase model (Tn5 transposase)	29
LEDGF/p75-integrase	374
Lysate	4
Melanoma inhibitor of apoptosis protein	20

TABLE 2 (*Continued*)

Target listed	Number of molecules
N-myristoyltransferase	1
NCp7	324
NCp7:SL3	4
NEF	394
Neuraminidase	5
Nuclear factor-kappa B	10
Nucleocapsid	79
P300/CBP-associated factor	22
Phosphodiesterase type IV	1
Positive transcription elongation factor b	1
Protease	18 209
Protein disulfide isomerase	17
Protein kinase A	7
Protein kinase C	7
REV	23
RNA polymerase II	2
RNase H	1818
Rev:RRE	395
Reverse transcriptase	22 959
Reverse transcriptase model (MMLV Reverse transcriptase)	30
Ribonucleotide reductase	2
SPC3	2
Tat	115
Tat:TAR/LTR	909
VIF	7
VPR	35
VPU	5
X-linked inhibitor of apoptosis protein	104
gp120	1175
gp160	26
gp41	392
p17	11

BEC3G can be increased in cells by defensins and chemokines that bind to CCR6 [82,83]. Furthermore, there is some evidence that the CCR6 ligand human beta defensin 2 can induce the transition from high-molecular-mass APOBEC3G complexes to the low-molecular-mass monomeric form [83].

Mucosa-associated lymphoid tissue translocation 1

Mucosa-associated lymphoid tissue translocation 1 (MALT1) inhibitors are being aggressively pursued for treating lymphomas, which occur with high incidence in HIV-infected subjects, and there are several publications describing the repurposing of drugs that show MALT1 inhibition [84,85]. We (Lafferty and Garzino-Demo, unpublished results) are pursuing MALT1 inhibitors as part of a 'block and kill' strategy to a functional cure to HIV (i.e., suppression of reactivation and induction of apoptosis of infected cells). A publication on the effects of the MALT1 inhibitor: MI-2, on a cell line that is used as an *in vitro* model of HIV latency showed accelerated cell death in the presence of cell stimuli [86].

Toll-like receptor 4

Toll-like receptors (TLRs) are known as pattern recognition receptors (PRRs) where the specific level of action depends on the infecting pathogen and they have central roles in the innate immune system, representing the first line of defense [87,88]. Past studies have also shown the ability of TLR4 to lower HIV-1 replication [89]. The chemokine response triggered by the infectious agent upon interaction with the macrophages of the host and role in the containment of HIV-1 infection in the main targets of the virus, T cells and mononuclear phagocytes was demonstrated decades ago. LPS stimulates human monocyte-derived macrophages (MDM) to release soluble factors that strongly inhibit HIV replication, not only in macrophages but also in T lymphocytes [90]. Recombinant human RANTES, MIP-1α and MIP-1β induced a dose-dependent inhibition of different strains of HIV-1, HIV-2 and simian immunodeficiency virus (SIV) [91]. Recently, a naturally derived polysaccharide peptide (PSP) from the fungus *Coriolus versicolor* [92] demonstrated anti-HIV activity producing antiviral chemokines that block co-receptors. PSP also upregulated TLR4 expression [93].

Y-box-binding protein 1

The DNA and RNA binding protein Y-box-binding protein 1 (YB-1) has been associated with a plethora of viruses [94]. YB-1 was shown to form a complex with the HIV Tat–TAR transcriptional complex [95] supporting HIV replication. YB-1 is an important cofactor of HIV replication that exerts its effects at two stages in a concentration-dependent manner. The early effect occurs at a stage between reverse transcription and nuclear import. The late effect involves viral RNA stability and virus production. This could hence represent a new antiviral target that affects multiple stages of viral replication [96].

B23/nucleophosmin

B23/nucleophosmin (B23/NPM1) is a multifunctional protein constantly shuttling between the nucleus and cytosol. This influences viral replication because it has a role in nuclear import, viral genome transcription and assembly, as well as final particle formation. A small number of B23/NPM1 inhibitors are available as potential broad-spectrum antivirals [97].

Natural seminal amyloids

Small peptides present in human semen aggregate into amyloid-like fibrils and can increase infectivity by >400 000 and can facilitate viral attachment and internalization. Interfering with these aggregates represents a potential target that could be used while also using other antiviral agents [98,99]. For example, the amyloid-binding benzothiazole aniline (BTA) molecules target β-sheet-rich structural features found in seminal amyloid species such as semen-derived enhancer of virus infection (SEVI) as well as in other amyloid aggregates [100]. The small molecule aminoquinoline surfen is another example of a SEVI-binding molecule that inhibits the interaction between SEVI and cellular and viral surfaces [101].

Concluding remarks

There are many targets that have been evaluated for treating HIV and for which many thousands of compounds have been tested *in vitro* (Table 2). We have briefly summarized newer targets for HIV that do not have FDA-approved drugs on the market to address this virus (Table 1). These targets represent a broad array of predominantly host proteins that could all be targeted with small molecules. Most of these targets have received little or no attention from the drug discovery community yet could be compelling even with all the attendant limitations of toxicity over long-term use. There is still a considerable need to find new drugs to address this virus and to create new intellectual property. Some of these newer drug targets are also useful for developing drugs for other viruses and could in turn represent broad-spectrum antiviral targets. The value of these targets will be determined in due course as drugs targeting them are approved by the FDA.

Conflicts of interest

A.C.P. is an employee and S.E. is owner of Collaborations Pharmaceuticals. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Acknowledgments

We kindly acknowledge NIH NINDS 1R01NS102164-01 and RFBR 17-54-30007. Research reported in this publication was supported by the National Institute of Neurological Disorders and Stroke of the National Institutes of Health under award number 1R01NS102164-01. Dr Thomas Lane and Ms Kim Zorn are kindly acknowledged for assistance with HIV research and preparing Table 1. Dr Mohamed Nasr is thanked for assistance with obtaining the NIAID ChemDB HIV, Opportunistic Infection and Tuberculosis Therapeutics Database.

References

1 Sharp, P.M. and Hahn, B.H. (2011) Origins of HIV and the AIDS pandemic. *Cold Spring Harb. Perspect. Med.* 1, a006841
2 WHO. (2018) HIV/AIDS.
3 Kinch, M.S. and Patridge, E. (2014) An analysis of FDA-approved drugs for infectious disease: HIV/AIDS drugs. *Drug Discov. Today* 19, 1510–1513
4 Tan, I.L. and McArthur, J.C. (2012) HIV-associated neurological disorders: a guide to pharmacotherapy. *CNS Drugs* 26, 123–134
5 Kolson, D. and Buch, S. (2013) More than two HANDs to tango. *J. Neuroimmune Pharmacol.* 8, 1051–1054
6 Kraft-Terry, S.D. *et al.* (2009) A coat of many colors: neuroimmune crosstalk in human immunodeficiency virus infection. *Neuron* 64, 133–145
7 Bertrand, L. *et al.* (2016) Solving the blood–brain barrier challenge for the effective treatment of HIV replication in the central nervous system. *Curr. Pharm. Des.* 22, 5477–5486
8 Rumbaugh, J.A. *et al.* (2008) Developing neuroprotective strategies for treatment of HIV-associated neurocognitive dysfunction. *Future HIV Ther.* 2, 271–280
9 Saylor, D. *et al.* (2016) HIV-associated neurocognitive disorder – pathogenesis and prospects for treatment. *Nat. Rev. Neurol.* 12, 309
10 Esposito, F. *et al.* (2012) HIV-1 reverse transcriptase still remains a new drug target: structure, function, classical inhibitors, and new inhibitors with innovative mechanisms of actions. *Mol. Biol. Int.* 2012, 586401
11 Friedrich, B.M. *et al.* (2011) Host factors mediating HIV-1 replication. *Virus Res.* 161, 101–114
12 Hutter, G. *et al.* (2009) Long-term control of HIV by CCR5 Delta32/Delta32 stem-cell transplantation. *N. Engl. J. Med.* 360, 692–698
13 Tebas, P. *et al.* (2014) Gene editing of CCR5 in autologous CD4 T cells of persons infected with HIV. *N. Engl. J. Med.* 370, 901–910
14 Lai, M.M. (1998) Cellular factors in the transcription and replication of viral RNA genomes: a parallel to DNA-dependent RNA transcription. *Virology* 244, 1–12
15 Rolando, M. and Buchrieser, C. (2014) Legionella pneumophila type IV effectors hijack the transcription and translation machinery of the host cell. *Trends Cell Biol.* 24, 771–778
16 Park, R.J. *et al.* (2017) A genome-wide CRISPR screen identifies a restricted set of HIV host dependency factors. *Nat. Genet.* 49, 193–203
17 Farzan, M. *et al.* (1999) Tyrosine sulfation of the amino terminus of CCR5 facilitates HIV-1 entry. *Cell* 96, 667–676
18 van den Boom, J. *et al.* (2012) 3′-Phosphoadenosine 5′-phosphosulfate (PAPS) synthases, naturally fragile enzymes specifically stabilized by nucleotide binding. *J. Biol. Chem.* 287, 17645–17655
19 Kamiyama, S. *et al.* (2003) Molecular cloning and identification of 3′-phosphoadenosine 5′-phosphosulfate transporter. *J. Biol. Chem.* 278, 25958–25963
20 Seibert, C. *et al.* (2002) Tyrosine sulfation of CCR5 N-terminal peptide by tyrosylprotein sulfotransferases 1 and 2 follows a discrete pattern and temporal sequence. *Proc. Natl. Acad. Sci. U. S. A.* 99, 11031–11036
21 Neira, J.L. (2009) Biophysical and structural studies on the capsid protein of the human immunodeficiency virus type 1: a new drug target? *ScientificWorldJournal* 9, 404–419
22 Cheng, N. *et al.* (2014) Development of a novel screening strategy designed to discover a new class of HIV drugs. *J. Lab. Autom.* 19, 297–303
23 Tian, Y.S. *et al.* (2013) Discovery of novel low-molecular-weight HIV-1 inhibitors interacting with cyclophilin A using *in silico* screening and biological evaluations. *J. Mol. Model.* 19, 465–475
24 Smith, P.F. *et al.* (2007) Phase I and II study of the safety, virologic effect, and pharmacokinetics/pharmacodynamics of single-dose 3-o-(3,3-dimethylsuccinyl) betulinic acid (bevirimat) against human immunodeficiency virus infection. *Antimicrob. Agents Chemother.* 51, 3574–3581
25 Wang, W. *et al.* (2017) Inhibition of HIV-1 maturation via small-molecule targeting of the amino-terminal domain in the viral capsid protein. *J. Virol.* 91, e02155–e02156
26 Lemke, C.T. *et al.* (2012) Distinct effects of two HIV-1 capsid assembly inhibitor families that bind the same site within the N-terminal domain of the viral CA protein. *J. Virol.* 86, 6643–6655
27 Sokolskaja, E. *et al.* (2004) Target cell cyclophilin A modulates human immunodeficiency virus type 1 infectivity. *J. Virol.* 78, 12800–12808
28 Li, J. *et al.* (2009) Discovery of dual inhibitors targeting both HIV-1 capsid and human cyclophilin A to inhibit the assembly and uncoating of the viral capsid. *Bioorg. Med. Chem.* 17, 3177–3188
29 Liu, C. *et al.* (2016) Cyclophilin A stabilizes the HIV-1 capsid through a novel non-canonical binding site. *Nat. Commun.* 7, 10714
30 Freedman, R.B. (1989) Protein disulfide isomerase: multiple roles in the modification of nascent secretory proteins. *Cell* 57, 1069–1072
31 Gallina, A. *et al.* (2002) Inhibitors of protein-disulfide isomerase prevent cleavage of disulfide bonds in receptor-bound glycoprotein 120 and prevent HIV-1 entry. *J. Biol. Chem.* 277, 50579–50588
32 Barbouche, R. *et al.* (2003) Protein-disulfide isomerase-mediated reduction of two disulfide bonds of HIV envelope glycoprotein 120 occurs post-CXCR4 binding and is required for fusion. *J. Biol. Chem.* 278, 3131–3136
33 Tsibris, J.C. *et al.* (1989) Selective inhibition of protein disulfide isomerase by estrogens. *J. Biol. Chem.* 264, 13967–13970
34 Khan, M.M. *et al.* (2011) Discovery of a small molecule PDI inhibitor that inhibits reduction of HIV-1 envelope glycoprotein gp120. *ACS Chem. Biol.* 6, 245–251
35 Bi, S. *et al.* (2011) Galectin-9 binding to cell surface protein disulfide isomerase regulates the redox environment to enhance T-cell migration and HIV entry. *Proc. Natl. Acad. Sci. U. S. A.* 108, 10650–10655
36 Curreli, F. *et al.* (2016) Design, synthesis and evaluation of small molecule CD4-mimics as entry inhibitors possessing broad spectrum anti-HIV-1 activity. *Bioorg. Med. Chem.* 24, 5988–6003
37 Melillo, B. *et al.* (2016) Small-molecule CD4-mimics: structure-based optimization of HIV-1 entry inhibition. *ACS Med. Chem. Lett.* 7, 330–334
38 Nekhai, S. *et al.* (2013) Role of cellular iron and oxygen in the regulation of HIV-1 infection. *Future Virol.* 8, 301–311
39 Liu, Y. *et al.* (2018) Lysine-specific demethylase 1 cooperates with BRAF-histone deacetylase complex 80 to enhance HIV-1 Tat-mediated transactivation. *Virus Genes* 54, 662–671

40 Lin, X. *et al.* (2017) Protein phosphatase-1-targeted small molecules, iron chelators and curcumin analogs as HIV-1 antivirals. *Curr. Pharm. Des.* 23, 4122–4132
41 Boyer, P.L. *et al.* (2018) Developing and evaluating inhibitors against the RNase H active site of HIV-1 reverse transcriptase. *J. Virol.* 92, e02203–e022017
42 Cuzzucoli Crucitti, G. *et al.* (2015) Structure-activity relationship of pyrrolyl diketo acid derivatives as dual inhibitors of HIV-1 integrase and reverse transcriptase ribonuclease H domain. *J. Med. Chem.* 58, 1915–1928
43 Corona, A. *et al.* (2017) Design, synthesis and antiviral evaluation of novel heteroarylcarbothioamide derivatives as dual inhibitors of HIV-1 reverse transcriptase-associated RNase H and RDDP functions. *Pathog. Dis.* 75, 78
44 Blokken, J. *et al.* (2017) Proteinprotein and proteinchromatin interactions of LEDGF/p75 as novel drug targets. *Drug Discov. Today Technol.* 24, 25–31
45 Bertoletti, F. *et al.* (2012) Tyrosine kinases as essential cellular cofactors and potential therapeutic targets for human immunodeficiency virus infection. *Cell Mol. Biol.* 58, 31–43
46 Phipps, D.J. *et al.* (1996) HIV infection *in vitro* enhances the activity of Src-family protein tyrosine kinases. *AIDS* 10, 1191–1198
47 McCarthy, S.D. *et al.* (2016) c-SRC protein tyrosine kinase regulates early HIV-1 infection post-entry. *AIDS* 30, 849–858
48 Percario, Z.A. *et al.* (2015) Nef, the shuttling molecular adaptor of HIV, influences the cytokine network. *Cytokine Growth Factor Rev.* 26, 159–173
49 Sauter, D. and Kirchhoff, F. (2018) Multilayered and versatile inhibition of cellular antiviral factors by HIV and SIV accessory proteins. *Cytokine Growth Factor Rev.* 40, 3–12
50 Pereira, E.A. and daSilva, L.L. (2016) HIV-1 Nef: taking control of protein trafficking. *Traffic* 17, 976–996
51 Selby, M.J. *et al.* (1989) Structure, sequence, and position of the stem-loop in tar determine transcriptional elongation by tat through the HIV-1 long terminal repeat. *Genes Dev.* 3, 547–558
52 Deeks, S.G. *et al.* (2013) The end of AIDS: HIV infection as a chronic disease. *Lancet* 382, 1525–1533
53 Razooky, B.S. *et al.* (2015) A hardwired HIV latency program. *Cell* 160, 990–1001
54 Karn, J. (2011) The molecular biology of HIV latency: breaking and restoring the Tat-dependent transcriptional circuit. *Curr. Opin. HIV AIDS* 6, 4–11
55 Ghose, R. *et al.* (2001) Induction of TAK (cyclin T1/P-TEFb) in purified resting CD4 (+) T lymphocytes by combination of cytokines. *J. Virol.* 75, 11336–11343
56 Kinoshita, S. *et al.* (1998) Host control of HIV-1 parasitism in T cells by the nuclear factor of activated T cells. *Cell* 95, 595–604
57 Nabel, G. and Baltimore, D. (1987) An inducible transcription factor activates expression of human immunodeficiency virus in T cells. *Nature* 326, 711–713
58 Tyagi, M. and Karn, J. (2007) CBF-1 promotes transcriptional silencing during the establishment of HIV-1 latency. *EMBO J.* 26, 4985–4995
59 He, G. and Margolis, D.M. (2002) Counterregulation of chromatin deacetylation and histone deacetylase occupancy at the integrated promoter of human immunodeficiency virus type 1 (HIV-1) by the HIV-1 repressor YY1 and HIV-1 activator Tat. *Mol. Cell Biol.* 22, 2965–2973
60 Lenasi, T. *et al.* (2008) Transcriptional interference antagonizes proviral gene expression to promote HIV latency. *Cell Host Microbe* 4, 123–133
61 Gao, W.Y. *et al.* (1993) Low levels of deoxynucleotides in peripheral blood lymphocytes: a strategy to inhibit human immunodeficiency virus type 1 replication. *Proc. Natl. Acad. Sci. U. S. A.* 90, 8925–8928
62 Mahmoudi, T. *et al.* (2006) The SWI/SNF chromatin-remodeling complex is a cofactor for Tat transactivation of the HIV promoter. *J. Biol. Chem.* 281, 19960–19968
63 Treand, C. *et al.* (2006) Requirement for SWI/SNF chromatin-remodeling complex in Tat-mediated activation of the HIV-1 promoter. *EMBO J.* 25, 1690–1699
64 Van Lint, C. *et al.* (2013) HIV-1 transcription and latency: an update. *Retrovirology* 10, 67
65 Cary, D.C. *et al.* (2016) Molecular mechanisms of HIV latency. *J. Clin. Invest.* 126, 448–454
66 Yukl, S. *et al.* (2009) Latently-infected CD4+ T cells are enriched for HIV-1 Tat variants with impaired transactivation activity. *Virology* 387, 98–108
67 Mousseau, G. *et al.* (2015) The Tat inhibitor didehydro-cortistatin A prevents HIV-1 reactivation from latency. *MBio* 6, e00465
68 Kessing, C.F. *et al.* (2017) *In vivo* suppression of HIV rebound by didehydro-cortistatin A, a block-and-lock strategy for HIV-1 treatment. *Cell Rep.* 21, 600–611
69 Lambert, A.A. *et al.* (2013) Dendritic cell immunoreceptor is a new target for anti-AIDS drug development: identification of DCIR/HIV-1 inhibitors. *PLoS One* 8, e67873
70 Besnard, E. *et al.* (2016) The mTOR complex controls HIV latency. *Cell Host Microbe* 20, 785–797
71 Heredia, A. *et al.* (2008) Reduction of CCR5 with low-dose rapamycin enhances the antiviral activity of vicriviroc against both sensitive and drug-resistant HIV-1. *Proc. Natl. Acad. Sci. U. S. A.* 105, 20476–20481
72 Gavegnano, C. *et al.* (2014) Ruxolitinib and tofacitinib are potent and selective inhibitors of HIV-1 replication and virus reactivation *in vitro*. *Antimicrob. Agents Chemother.* 58, 1977–1986
73 Gavegnano, C. *et al.* (2017) Novel mechanisms to inhibit HIV reservoir seeding using Jak inhibitors. *PLoS Pathog.* 13, e1006740
74 Zheng, Y. *et al.* (2011) Host protein Ku70 binds and protects HIV-1 integrase from proteasomal degradation and is required for HIV replication. *J. Biol. Chem.* 286, 17722–17735
75 Pagans, S. *et al.* (2005) SIRT1 regulates HIV transcription via Tat deacetylation. *PLoS Biol.* 3, e41
76 Kwon, H.S. *et al.* (2008) Human immunodeficiency virus type 1 Tat protein inhibits the SIRT1 deacetylase and induces T cell hyperactivation. *Cell Host Microbe* 3, 158–167
77 Hardie, D.G. (2007) AMP-activated/SNF1 protein kinases: conserved guardians of cellular energy. *Nat. Rev. Mol. Cell Biol.* 8, 774–785
78 Sanz, P. (2008) AMP-activated protein kinase: structure and regulation. *Curr. Protein Pept. Sci.* 9, 478–492
79 Zhang, H.S. and Wu, M.R. (2009) SIRT1 regulates Tat-induced HIV-1 transactivation through activating AMP-activated protein kinase. *Virus Res.* 146, 51–57
80 Ara, A. *et al.* (2017) Mechanism of enhanced HIV restriction by virion coencapsidated cytidine deaminases APOBEC3F and APOBEC3G. *J. Virol.* 91, e02230–e02236
81 Izumi, T. *et al.* (2008) Cytidine deaminases as a weapon against retroviruses and a new target for antiviral therapy. *Mini Rev. Med. Chem.* 8, 231–238
82 Lafferty, M.K. *et al.* (2010) CCR6 ligands inhibit HIV by inducing APOBEC3G. *Blood* 115, 1564–1571
83 Lafferty, M.K. *et al.* (2017) Human beta defensin 2 selectively inhibits HIV-1 in highly permissive CCR6(+)CD4(+) T cells. *Viruses* 9 . http://dx.doi.org/10.3390/v9050111
84 Wu, G. *et al.* (2018) Synthesis and structure-activity relationship studies of MI-2 analogues as MALT1 inhibitors. *Bioorg. Med. Chem.* 26, 3321–3344
85 Schlapbach, A. *et al.* (2018) *N*-aryl-piperidine-4-carboxamides as a novel class of potent inhibitors of MALT1 proteolytic activity. *Bioorg. Med. Chem. Lett.* 28, 2153–2158
86 Li, H. *et al.* (2016) Short communication: preferential killing of HIV latently infected CD4(+) T cells by MALT1 inhibitor. *AIDS Res. Hum. Retroviruses* 32, 174–177
87 Suresh, R. and Mosser, D.M. (2013) Pattern recognition receptors in innate immunity, host defense, and immunopathology. *Adv. Physiol. Educ.* 37, 284–291
88 Altfeld, M. and Gale, M., Jr (2015) Innate immunity against HIV-1 infection. *Nat. Immunol.* 16, 554–562
89 Swaminathan, G. *et al.* (2012) A role for microRNA-155 modulation in the anti-HIV-1 effects of Toll-like receptor 3 stimulation in macrophages. *PLoS Pathog.* 8, e1002937
90 Verani, A. *et al.* (1997) C-C chemokines released by lipopolysaccharide (LPS)-stimulated human macrophages suppress HIV-1 infection in both macrophages and T cells. *J. Exp. Med.* 185, 805–816
91 Cocchi, F. *et al.* (1995) Identification of RANTES, MIP-1 alpha, and MIP-1 beta as the major HIV-suppressive factors produced by CD8+ T cells. *Science* 270, 1811–1815
92 Collins, R.A. and Ng, T.B. (1997) Polysaccharopeptide from *Coriolus versicolor* has potential for use against human immunodeficiency virus type 1 infection. *Life Sci.* 60, PL383–PL387
93 Rodriguez-Valentin, M. *et al.* (2018) Naturally derived anti-HIV polysaccharide peptide (PSP) triggers a Toll-like receptor 4-dependent antiviral immune response. *J. Immunol. Res.* 2018, 8741698
94 Kawaguchi, A. *et al.* (2012) YB-1 functions as a porter to lead influenza virus ribonucleoprotein complexes to microtubules. *J. Virol.* 86, 11086–11095
95 Ansari, S.A. *et al.* (1999) Interaction of YB-1 with human immunodeficiency virus type 1 Tat and TAR RNA modulates viral promoter activity. *J. Gen. Virol.* 80, 2629–2638
96 Weydert, C. *et al.* (2018) Y-box-binding protein 1 supports the early and late steps of HIV replication. *PLoS One* 13, e0200080
97 Lobaina, Y. and Perera, Y. (2019) Implication of B23/nucleophosmin in viral infections, potential uses of B23/NPM1 inhibitors as antiviral therapy. *Infect. Disord. Drug Targets* 19, 2–16
98 Sheik, D.A. *et al.* (2017) Natural seminal amyloids as targets for development of synthetic inhibitors of HIV transmission. *Acc. Chem. Res.* 50, 2159–2166

99 Hauber, I. *et al.* (2009) The main green tea polyphenol epigallocatechin-3-gallate counteracts semen-mediated enhancement of HIV infection. *Proc. Natl. Acad. Sci. U. S. A.* 106, 9033–9038

100 Olsen, J.S. *et al.* (2010) Amyloid-binding small molecules efficiently block SEVI (semen-derived enhancer of virus infection)- and semen-mediated enhancement of HIV-1 infection. *J. Biol. Chem.* 285, 35488–35496

101 Roan, N.R. *et al.* (2010) Aminoquinoline surfen inhibits the action of SEVI (semen-derived enhancer of viral infection). *J. Biol. Chem.* 285, 1861–1869

102 Zhou, W. *et al.* (2017) A fluorescence-based high-throughput assay to identify inhibitors of tyrosylprotein sulfotransferase activity. *Biochem. Biophys. Res. Commun.* 482, 1207–1212

103 Byrne, D.P. *et al.* (2018) New tools for evaluating protein tyrosine sulfation: tyrosylprotein sulfotransferases (TPSTs) are novel targets for RAF protein kinase inhibitors. *Biochem. J.* 475, 2435–2455

104 Sticht, J. *et al.* (2005) A peptide inhibitor of HIV-1 assembly *in vitro*. *Nat. Struct. Mol. Biol.* 12, 671–677

105 Thenin-Houssier, S. *et al.* (2016) Ebselen, a small-molecule capsid inhibitor of HIV-1 replication. *Antimicrob. Agents Chemother.* 60, 2195–2208

106 Romashov, L.V. and Ananikov, V.P. (2016) Synthesis of HIV-1 capsid protein assembly inhibitor (CAP-1) and its analogues based on a biomass approach. *Org. Biomol. Chem.* 14, 10593–10598

107 Fujioka, T. *et al.* (1994) Anti-AIDS agents, 11. Betulinic acid and platanic acid as anti-HIV principles from *Syzigium claviflorum*, and the anti-HIV activity of structurally related triterpenoids. *J. Nat. Prod.* 57, 243–247

108 George, A. *et al.* (2018) 1,2,3,4-Tetrahydroisoquinolines as inhibitors of HIV-1 integrase and human LEDGF/p75 interaction. *Chem. Biol. Drug Des.* 91, 1133–1140

109 Zhang, F.H. *et al.* (2017) Discovery of novel 3-hydroxypicolinamides as selective inhibitors of HIV-1 integrase-LEDGF/p75 interaction. *Eur. J. Med. Chem.* 125, 1051–1063

110 Patel, P.A. *et al.* (2016) Indole-based allosteric inhibitors of HIV-1 integrase. *Bioorg. Med. Chem. Lett.* 26, 4748–4752

111 Smithgall, T.E. and Thomas, G. (2013) Small molecule inhibitors of the HIV-1 virulence factor. *Nef. Drug Discov. Today Technol.* 10, e523–e529