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New targets for HIV drug discovery

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Abstract

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.

Keywords

Drug discovery; HIV; host targets; virus targets; drug candidates

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

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Teaser: We describe more than 20 targets that can be addressed by small-molecule treatments that could overcome HIV drug resistance as well as provide a potential cure.

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.

HIV-related illnesses in 2017 alone [2]. Currently, approved HIV drugs target reverse transcriptase (RT), HIV protease and integrase, the C–C motif chemokine receptor type 5 (CCR) 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 (MIP)-1 α , MIP-1 β 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]. 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 clinical trial Phase II, 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 CAP 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 IC₅₀ 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, MHC-I, CD28, CD3 (HIV-2 and most SIVs), 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/PTEFb) [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 APOBEC3G 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-1 α and MIP-1 β 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.

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Highlights:

- HIV kills close to one million people
- There is a need for new treatments to address drug resistance
- There are many newer targets that could be targeted with small molecules
- Over 20 of these targets are discussed with references to work, to date
- Some of these targets could also lead to broad-spectrum antivirals

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	<u>3AP1</u> , <u>3AP2</u> , <u>3AP3</u>
SLC35B2	Host	Entry		
ALCAM	Host	Spread of HIV infection		
Gag, capsid	Virus	Entry	[22–26,104–107] ChEMBL2366504 ChEMBL3800 ChEMBL3638360 ChEMBL378	514T, <u>6ES8</u> , <u>3BQ</u> , <u>3J34</u> , <u>5MD7</u> , <u>5MCY</u> , <u>3P0A</u>
Cyclophilin A	Host		[28] ChEMBL1949	1RMH, 1AK4, 1AWR, 1FGL, 1M9C, 5FJB, 5LUD, 5NOS, 5T9U, 6GJI, 6GJI, 6GJI, 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	<u>3LP3</u> , <u>3QIP</u> , <u>4QAG</u> , <u>3IGL</u> , <u>3QLH</u> , <u>6ELI</u> , <u>5JIE</u> , <u>3K2P</u> , <u>2ISL</u> , <u>5UV5</u> , <u>6AOC</u> , <u>1HRH</u>
LEDGF/p75	Host	Transcription	[108–110] PubChem AID: 1053136	2B4I, 3F9K, 5OYM
c-SRC protein tyrosine kinase	Host	Early stages of virus entry	[47] ChEMBL986499	4MXO, 3VRO, 1FMK, 1Y57, 1YOL, 1YOM, 2BDI, 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, <u>3MI9</u> , 3MIA

Target	Location	Mechanism	Small molecule inhibitor references, datasets in ChEMBL and PubChem	Representative structures
Dendritic cell immunoreceptor	Host	Infection/propagation	[69]	5B1W , 5B1X
mTOR pathway	Host	Transcription	[70] ChEMBL2842 ChEMBL2221341 PubChem AID: 493208 PubChem AID: 504465	
IAK 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 , 4IIR , 3UO8 , 4IIP
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]	2PIB , 5EHD
Natural seminal amyloids	Host	Entry inhibitor	[100, 101]	3PPD , 2L3H

Abbreviation: N/A, not applicable.

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

Table 2.

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

Target listed	Number of molecules
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
W-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

Target listed	Number of molecules
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
RNaseH	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