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Cancer Therapies in HIV Cure Research

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Abstract

Purpose of review—To provide an overview of anti-cancer therapies in various stages of clinical development as potential interventions to target HIV persistence

Recent findings—Epigenetic drugs developed for cancer have been investigated *in vitro*, *ex vivo* and in clinical trials as interventions aimed at reversing HIV latency and depleting the amount of virus that persists on antiretroviral therapy (ART). Treatment with histone deacetylase inhibitors induced HIV-expression in patients on ART but did not reduce the frequency of infected cells. Other interventions that may accelerate the decay of latently infected cells, in the presence or absence of latency-reversing therapy, are now being explored. These include apoptosis-promoting agents, non-HDACi compounds to reverse HIV latency and immunotherapy interventions to enhance antiviral immunity such as immune checkpoint inhibitors and toll-like receptor agonists.

Summary—A curative strategy in HIV will likely need to both reduce the amount of virus that persists on ART and improve anti-HIV immune surveillance. While we continue to explore advances in the oncology field including cancer immunotherapy, there are major differences in the risk-benefit assessment between HIV infected and patients with malignancies. Drug development specifically targeting HIV persistence will be key to developing effective interventions with an appropriate safety profile.

Keywords

HIV latency; HIV reservoir; HIV cure; apoptosis-promoting agents; immune checkpoint inhibitors

Introduction

Although HIV infection and malignancies are fundamentally different disease processes, there are important similarities when considering strategies to cure HIV or allow for

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Conflicts of interest

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antiretroviral therapy (ART)-free remission. The primary barrier to curing HIV is the long-term persistence of replication-competent virus in latently infected cells in HIV-infected individuals on ART [1]. Latency occurs at a very low frequency of around 60 infected cells per million resting CD4+ T cells in peripheral blood and at higher frequency in lymphoid tissue [2, 3]. Other mechanisms may also contribute significantly to long-term viral persistence including infection of non-CD4+ T cells [4], clonal expansion of replication-competent proviruses [5], low-level residual replication in tissues with insufficient penetration of ART [6, 7] or persistence in tissue sites where cytotoxic T cells (CTLs) have restricted access, including lymph node follicles [8]. One of the key challenges in both cancer and HIV cure research is the development of assays that allow detection of the rare cells with the capacity to rekindle infection or cause relapsing malignant disease. Epigenetic modifying drugs, originally developed for uses in oncology, are being evaluated in HIV cure research as a mechanism to reverse HIV latency and drugs that promote apoptosis are being evaluated to deplete infected cells. Finally, the recent development of immune-based therapies in cancer such as immune checkpoint (IC) inhibitors is another area of converging interest, i.e. interventions to enhance the immune response against HIV or cancer antigens.

Here we provide an overview of therapies developed for treating malignancies, which are now being investigated as potential interventions to target HIV persistence (Table 1). We will discuss these approaches and the relevant mechanisms and offer our view on their potential applicability in the onward search for an HIV cure (summarised in Figure 1). Although bone marrow transplantation for haematological malignancy has had a clear profound effect on reducing the frequency of latently infected cells and also increased ART-free remission, these interventions will not be discussed here.

Histone deacetylase inhibitors

Using latency reversing agents (LRAs) to activate HIV production in latently infected cells and potentially facilitate their elimination through virus- or immune-mediated cell lysis has been proposed as a strategy to target persistent HIV. Histone deacetylase inhibitors (HDACi), largely licensed for treating haematological malignancies, have now been studied in multiple small single-arm clinical trials as LRAs. The primary focus has been with vorinostat and romidepsin both approved for the treatment of cutaneous T cell lymphoma, and panobinostat, recently licensed for multiple myeloma. Early-phase clinical trials with vorinostat [9, 10], panobinostat [11] and romidepsin [12] have all demonstrated increases in HIV transcription, and in some cases also plasma HIV RNA. However, this did not reduce the frequency of latently infected CD4+ T cells. Current efforts are therefore focused on using HDACi in combination with other strategies that enhance HIV transcription, such as other epigenetic modifying drugs or with strategies that enhance HIV-specific immunity via therapeutic vaccination [13] (NCT02336074, NCT02616874), pegylated interferon (NCT02471430) and antigen loaded dendritic cells (NCT02707900).

Protein kinase C agonists

Activation of protein kinase C (PKC) with prostratin was originally shown to potently activate latent HIV *in vitro* [14], but given its toxicity it is uncertain whether this drug will

proceed to clinical studies. Bryostatins are another PKC agonist and are in clinical development for malignancies including multiple myeloma and renal cell carcinoma [15]. Bryostatins activated HIV latency in resting CD4⁺ T cells from HIV-infected individuals on ART and when combined with potent HDACi displayed strong synergy and induced HIV production similar to maximal T cell stimulation [16]. However, a recent clinical trial using bryostatin-1 in HIV-infected individuals on ART did not demonstrate any effect on either PKC activity or HIV transcription, likely due to the low plasma concentrations observed with the doses used [17]. Ingenol derivatives also activate PKC isoforms, leading to increased NF- κ B nuclear translocation and subsequent HIV RNA transcription. Ingenol B (IngB) was more efficient in inducing viral transcription in infected primary CD4 T cells than vorinostat, hexamethylene bisacetamide (HMBA) or mitogenic stimuli [18]. These agents have potential clinical utility in HIV cure trials but adverse events related to immune activation are of potential concern.

Bromodomain inhibitors

Bromodomain and extra-terminal (BET) proteins play a key role in the epigenetic regulation of gene expression by regulating the recruitment of cellular transcription factors [19]. As bromodomain proteins are implicated in cancer [19], BET inhibitors are being investigated for the treatment of multiple malignancies, with 14 BET inhibitors currently in clinical trials. Whereas the initial focus was haematological malignancies such as leukaemia, lymphoma and multiple myeloma, ongoing phase 1/2 trials are evaluating BET inhibitors in a range of solid tumours [20]. The BET proteins BRD2 and BRD4 repress HIV transcription during latency by inhibiting transcriptional initiation or by binding positive transcription elongation factor b (P-TEFb) in resting CD4⁺ T-cells [19, 21]. Consequently, bromodomain inhibitors are now being explored for their ability to reverse HIV latency. JQ1, i-BET, i-BET151 and MS417 BET inhibitors activated latent HIV in cell lines and some primary CD4⁺ T-cell latency models, but showed modest or no activity *ex vivo* in resting CD4⁺ T-cells from HIV-infected individuals on ART [16, 22, 23]. Moreover, these compounds are not yet in clinical trials in oncology so their associated toxicities in the clinical setting are unknown.

Another BET inhibitor, OTX015, is currently in phase 1 and 1b trials for haematological malignancies and solid tumours including prostate, breast, and lung cancer [24]. OTX015 induced HIV production in resting CD4⁺ T-cells from HIV-infected individuals on ART [25] and both OTX015 [25] and JQ1 [16, 22] displayed synergy *ex vivo* when combined with low dose protein kinase C (PKC) agonists. Overall, BET inhibitors clearly have pharmacological potential to activate HIV from latency, which may be enhanced in combination with other LRAs, but the current lack of clinical safety and pharmacokinetic data is likely to limit their immediate development for HIV cure studies.

DNA Methyltransferase Inhibitors

DNA methylation at gene promoters is regulated by DNA methyltransferases (DNMT) leading to transcriptional silencing. These pathways are relevant to myelodysplastic syndromes and malignancies including acute myeloid leukemia [26]. Consequently, DNMT inhibitors have undergone clinical development with 5-azacitidine (azacitidine) and 5-

aza-2'-deoxycytidine (decitabine) now licensed for the treatment of myelodysplastic syndrome and SGI-110 is in a range of clinical trials for various malignancies [26, 27]. Because hypermethylation around the HIV promoter is associated with repression of HIV transcription, DNMT inhibitors are also being investigated for their effect on HIV latency [28]. The DNMT inhibitors decitabine and zebularine activated HIV transcription in latently infected cell lines when combined with other LRAs [29, 30], and decitabine also activated HIV transcription in resting CD4+ T-cells from an aviremic patient on ART with high HIV CpG hypermethylation [29]. However, the overall low frequency of methylation at the HIV promoter in CD4+ T cells from HIV-infected individuals on ART [29] may limit the efficacy of DNMT inhibitors in HIV, and more studies are needed to explore their potential in combination with low doses of tolerable LRAs such as HDACi and disulfiram.

Apoptosis Inducers

Apoptosis, or programmed cell death, eliminates cells that are stressed, damaged or no longer required. Apoptosis is triggered by numerous signals through two main pathways: the extrinsic or intrinsic [31]. The extrinsic pathway is triggered by ligand binding to cell-surface death receptors, whereas the intrinsic pathway is triggered by intracellular stress signals leading to mitochondrial release of cytochrome *c*, second mitochondria-derived activator of caspase (SMAC) and Omi into the cytosol to trigger apoptosis. Both extrinsic and intrinsic pathways culminate in a proteolytic caspase cascade that induces apoptosis [31]. Apoptosis is regulated by members of the BCL-2 protein family plus inhibitor of apoptosis (IAP) proteins including XIAP, cIAP1 and cIAP2 [31, 32]. Inhibitors of apoptosis regulatory proteins, like the anti-apoptotic BCL-2 family of proteins, can trigger cell death and are under clinical development to target malignancies. In HIV cure research, such agents could be exploited to eliminate latently infected cells, avoiding the need for boosting or altering immune-mediated clearance. Combining these inducers of apoptosis with LRAs may potentially lead to selective death of latently infected cells if the apoptotic pathway is triggered by HIV RNA or proteins. Several classes of drugs that induce apoptosis could be relevant to HIV cure, some of which are detailed below.

i. BCL-2 inhibitors

Venetoclax (Venclexta/ABT-199), an oral and highly selective BCL-2 inhibitor, was recently licensed for the treatment of chronic lymphocytic leukaemia [33] and was shown to selectively enhance apoptosis of latently infected CD4+ T-cells *in vitro* following activation with anti-CD3/anti-CD28 [34]. This approach exploited the known interaction between the caspase cleavage peptide Casp8p41, generated by the viral protease, and the cellular protein BAK (which enhances apoptosis) or BCL-2 (which inhibits apoptosis) [34]. Pre-treating T cells from HIV infected individuals on ART *ex vivo* with venetoclax followed by maximal T cell stimulation induced preferential apoptosis and depleted HIV-infected cells in 8 of 11 patients [34]. Notably, venetoclax did not reduce the viability of CD4+ T-cells in the absence of T cell stimulation. Further investigation of venetoclax using LRAs with less toxicity than maximal T cell stimulation is required to determine if similar synergy is observed. Other inhibitors targeting BCL-2 or other apoptosis regulators (*eg.* obatoclax/GX15-070 currently

in clinical trials) could also be examined to pre-sensitise cells to apoptosis before reactivation of latent HIV.

ii. RIG-I Inducers

Another pathway that can trigger apoptosis is through retinoic acid-inducible gene I (RIG-I). RIG-I detects intracellular viral RNA and induces interferon-mediated apoptosis. This pathway can be activated by acitretin, a retinoic acid derivative with activity in non-melanoma skin cancer [35] and approved for the management of severe psoriasis [36]. When acitretin was added to latently infected cell lines or CD4+ T cells from HIV infected individuals on ART, acitretin not only stimulated HIV transcription but also induced RIG-I signalling and the pro-apoptotic BAX protein leading to preferential apoptosis of reactivated cells [37]. Acitretin also stimulated HIV transcription through activation of p300 histone acetyltransferase and this effect was enhanced in the presence of the HDACi vorinostat [37]. This new strategy represents an interesting concept of combining latency reversal with augmented sensing of intracellular viral RNA, potentially enhancing the selective death of virus-producing cells.

iii. IAP Inhibitors – SMAC Mimetics

By antagonising cellular inhibitors of apoptosis proteins (cIAPs), SMAC mimetics promote TNF-mediated cell death and are currently being investigated in numerous phase 1 and phase 2 studies of haematological malignancies and solid tumours [38]. SMAC mimetics may also play a role in cure strategies for HIV although this research is still at an early stage. Depletion of the cIAP BIRC2 by SMAC mimetics induced HIV-expression in cell lines and, when combined with the HDACi panobinostat, had synergistic activity in CD4+ T cells isolated from HIV-infected individuals on ART [39]. The SMAC mimetic birinipant was originally developed for the management of chronic myeloid leukemia, but was recently shown to have no activity in a recent phase 2 study. Birinipant is also in clinical trials for ovarian cancer [40]. In mice infected with hepatitis B virus (HBV), which establishes chronic persistent infection on antiviral therapy, birinipant specifically eliminated HBV infected hepatocytes [41]. More work is required to investigate apoptosis-promoting effects of IAP inhibitors in HIV latency, but it is possible that SMAC mimetics such as birinipant could be useful in targeting latent HIV, particularly given the upregulation of the molecule XIAP in latently infected cells [42].

iv. PI3K/Akt Inhibitors

Dysregulation of phosphoinositide 3-kinase (PI3K) signalling proteins has been implicated in numerous cancers and inhibitors of the key upstream pathway factors, PI3K and Akt, are being explored as potential therapies for targeting a wide range of malignancies including haematological cancers and solid tumours [43]. Inhibiting this pro-survival pathway using PI3K or Akt inhibitors might also promote apoptosis of virus-producing cells but so far there is limited evidence for this effect. The Akt inhibitors miltefosine, perifosine and edelfosine blocked HIV-induced Akt activation and enhanced death of HIV-infected primary human macrophages or a human microglial cell line, [44]. Moreover, arctigenin, lancemaside A1 and compound K, which inhibit different components of the PI3K/Akt pathway, also blocked the pro-survival activity of the HIV protein Tat and increased death of a microglial

cell line [45]. These studies demonstrate that PI3K and Akt inhibitors can overcome the pro-survival activities of HIV Tat, but much more work is needed to clarify the potential of these compounds to target latently infected cells and, hence, their future place in cure research remains speculative at present.

Immune checkpoint inhibitors

Upregulation of inhibitory signalling through ICs on CD4+ and CD8+ T cells allows malignant cells to evade immune destruction and, therefore, monoclonal antibodies to block ICs have been developed to enhance anti-tumour immune responses [46]. Monoclonal antibodies against cytotoxic T-lymphocyte-associated protein 4 (CTLA-4; ipilimumab) and programmed death 1 (PD1; nivolumab and pembrolizumab) were the first to show efficacy in cancer and are now licensed for the treatment of melanoma and non-small cell lung cancer (NSCLC) [47, 48]. Furthermore, the use of these antibodies together for melanoma has shown enhanced efficacy, but also increased toxicity [49]. Interestingly, it was recently demonstrated that by modulating T cell chemokine expression, HDACi can enhance the anti-tumour response to anti-PD1 [50]. This concept is currently being tested in a phase 1b/2 clinical trial using the HDACi entinostat in combination with pembrolizumab (anti-PD1) in patients with NSCLC (NCT02437136), and could be highly relevant for the design of future combination studies in HIV cure.

Similar to malignant disease, HIV infection is characterised by increased expression of IC, which is associated with T cell exhaustion and disease progression [51, 52] and may constitute a mechanism for immune escape [53]. Therefore, IC blockade has attracted considerable interest as a strategy to enhance HIV specific T cell responses against virus-expressing cells, supported by previous studies showing that blocking CTLA-4 or PD1 can enhance HIV- and SIV-specific T cell function ex vivo [54, 55]. Furthermore, CD4+ T cells from HIV-infected individuals on ART that express the IC molecule PD1 are highly enriched for integrated HIV DNA and infectious virus in blood [56, 57] and in lymph node follicles [3]. Other IC molecules may also be important for identifying persistent HIV, and this was confirmed by a recent study showing a higher frequency of HIV infection in CD4+ T cells expressing PD1, T cell immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domain (TIGIT) and lymphocyte activation gene 3 (LAG-3) [58]. Collectively, these studies demonstrate that IC expression, in particular PD1, plays a key role in HIV persistence and might also explain why activating T cell function through IC blockade could activate expression of latent HIV, as we recently demonstrated in an HIV infected individual on ART with melanoma who underwent treatment with ipilimumab for malignancy [59].

The only clinical trial thus far to investigate IC blockade in HIV infected individuals on ART without malignancy was a dose-escalation study of BMS-936559, a monoclonal antibody to PD1 ligand1 (PD-L1). Data from the first dose showed an increase in HIV-specific CD8+ T cell responses in two of six individuals treated with a single infusion of low-dose (0.3 mg/kg) anti-PD-L1 but no effect on plasma or cell-associated HIV RNA [60]. Hypophysitis 36 weeks after receiving low-dose anti-PD-L1 was seen in one individual, which raised concern whether the risks of adverse effects with IC blockade could preclude their investigational use in HIV-infected individuals without cancer. Treatment with IC

inhibitors can cause a unique spectrum of immune-related adverse events (irAEs) in skin, gut, lung, kidney, liver or the endocrine system [61]. The frequency of irAEs is well described in oncology and rates of grade 3 or 4 irAEs have been relatively low at around 2% in studies with nivolumab or pembrolizumab, although slightly higher for ipilimumab, and considerably higher when ipilimumab and nivolumab were combined [49, 61]. Still, with sufficient monitoring most irAEs are reversible and can be managed fairly easy with glucocorticoids [62]. Notably, no cases of hypophysitis were reported in a phase 1 trial where 207 patients received anti-PD-L1 therapy over 12 weeks [63]. In conclusion, IC blockade represents a highly interesting immune-based intervention in HIV cure research that warrants further investigation. Gathering more robust data on safety and the effect on HIV latency and HIV-specific immunology in infected individuals receiving immunotherapy for management of cancer will be key to advancing this agenda. Two National Cancer Institute (NCI)-sponsored clinical trials, which are currently recruiting study participants, are particularly relevant in this context. These are a phase I dose-escalation study of nivolumab in combination with ipilimumab in patients with HIV-associated solid tumours (NCT02408861), and a phase I study of pembrolizumab in HIV infected individuals with relapsed, refractory or disseminated malignancies (NCT02595866). Both trials have safety as their primary outcome measure but do also investigate effects on HIV latency and the frequency of latently infected cells.

Other strategies that could boost HIV-specific T cell function being explored in cancer and which may be relevant to HIV cure include interleukin (IL)-15 and related agonists [64], IL-21 [65], bi-specific antibodies [66] and chimeric antigen receptor (CAR) T cells [67].

Toll-like receptor agonists

Innate immune recognition of foreign pathogens occurs through binding of pathogen-associated molecular patterns (PAMP) to pattern-recognition receptors (PRR) on innate immune cells including the family of toll-like receptors (TLR) [68]. Similarly, during tumour cell death, damage-associated molecular pattern molecules (DAMP) are dispersed, which may also bind to TLR and induce tumour-directed innate immune activation [69]. Consequently, TLR agonists are in development with phase 2 or 3 trials in lung cancer, melanoma, breast cancer and colorectal cancer [70]. In HIV research, TLR agonists have recently attracted attention because they activate antigen-presenting cells (APC) and augment priming of T cells and induce NK cell activation [71, 72]. Most studies have focused on agonists to TLR7 and TLR9, which are both expressed intracellularly on endolysosomes, with TLR7 in plasmacytoid dendritic cells (pDCs) and conventional DCs, and TLR9 in pDCs and B cells [73]. Several *in vitro* studies also suggested that some TLR agonists could activate HIV from latency [74, 75].

MGN1703, a novel TLR9 agonist, induced antiviral innate immune responses and boosted NK cell-mediated viral inhibition *in vitro* [71]. Based on these findings, MGN1703 is being investigated in a phase 1b/2a trial in 15 ART-suppressed HIV infected individuals, where preliminary data showed that MGN1703 given twice weekly over 4 weeks led to activation of pDCs, NK cells and T cells and an increase in plasma levels of interferon- α [76]. MGN1703 is currently being investigated in phase 3 trials for colorectal cancer [77].

The oral TLR7 agonists, GS-9620 and GS-986 have been administered to ART-suppressed simian immunodeficiency virus (SIV)-infected rhesus macaques and induced consistent increases in plasma viral RNA and T cell activation [78]. Moreover, two of nine TLR7-treated monkeys had no inducible virus in blood and lymph node tissue and these two animals also displayed virological control for at least 3–4 months when ART was withdrawn [78]. GS-9620 is now in a phase 1 trial in HIV infected individuals on ART.

Conclusion

Translational and clinical research in the HIV cure arena over the past decade has been inspired by drug development in the oncology field. A lot of work has been done to identify new LRAs in addition to HDACi, which have been extensively explored. However, LRAs other than HDACi that have been characterised to date also do not target HIV infected cells specifically. Therefore, significant concerns remain with respect to off target effects, long-term cancer risk and toxicity. Recent advances in cancer immunotherapy has revolutionised the treatment of some malignancies, and it is becoming increasingly clear that improvements in anti-HIV immunity will also be key to achieving ART-free remission. However, the favourable long-term prognosis of someone living with HIV compared to most malignancies means that the risks associated with new interventions need to be assessed with great caution. While we may continue to learn from and apply advances from the oncology field, developing new strategies that specifically target HIV persistence and have an acceptable safety profile remains a top priority.

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Key points

- Drugs developed for treating malignancies are being actively investigated as potential therapies to target HIV persistence
- Histone deacetylase inhibitors have been employed in clinical trials in HIV infected individuals on ART and activated HIV transcription but on their own, did not reduce the frequency of latently infected CD4+ T cells
- Other oncology drug classes are now being explored *in vitro* and *ex vivo* for their capacity to augment latency reversal or promote killing of virus-producing cells
- Immunomodulation with immune checkpoint inhibitors and toll-like receptor agonists appear to be promising in pre-clinical models of HIV latency and results from clinical trials are eagerly awaited

Figure 1. Anti-cancer compounds with potential to target HIV persistence

Latency reversing agents (LRAs) that induce HIV expression in latently infected cells include histone deacetylase inhibitors (HDACi), bromodomain and extra-terminal (BET) inhibitors, methylation inhibitors and protein kinase C (PKC) agonists. HDACi promote histone acetylation and chromatin remodelling at the HIV promoter to support access for transcription initiation. Methylation inhibitors prevent deleterious hypermethylation of CpG islands near the HIV promoter to foster HIV transcription initiation. PKC agonists (*eg.* prostratin, bryostatin) promote the accumulation of active cellular NF- κ B transcription factor in the cell nucleus to promote HIV transcription initiation. Bromodomain inhibitors (*eg.* JQ1) prevent PTEF-b binding to bromodomain proteins, releasing free PTEF-b to interact with HIV Tat protein for efficient HIV transcription elongation. Apoptosis-inducing compounds act on various pathways leading to caspase activation and apoptosis and could also be administered with LRAs to sensitise cells for apoptosis. For instance, acitretin triggers retinoic acid-inducible gene I (RIG-I) that in turn detects viral RNA for subsequent interferon-induced apoptosis. SMAC mimetics block inhibitor of apoptosis (IAP) proteins, preventing IAPs from inhibiting apoptosis and sensitizing cells towards apoptosis. Similarly, inhibitors of BCL-2 (*eg.* Venetoclax) block this BCL-2 inhibitor of apoptosis, sensitising cells towards apoptosis. Inhibitors of the PI3K/Akt pro-survival pathway both culminate in preventing Akt activation (which inhibits apoptosis), thereby also sensitising cells towards apoptosis. Immune-based therapies such as immune checkpoint (IC) inhibitors and toll-like

receptor (TLR) agonists may enhance immune-mediated killing of HIV-expressing cells. IC inhibitors (e.g. anti-PD1 or anti-CTLA-4) also block negative signalling to T cells and may potentially also reverse latency. TLR 7/9 agonists bind to receptors on endolysosomes in antigen-presenting cells and other immune cells, activate dendritic cells (DCs) and natural killer (NK) cells and induce release of interferon- α .

SMAC: second mitochondria-derived activator of caspase, PI3Ki: phosphoinositide 3-kinase inhibitor, Akti: Akt inhibitor, BCL-2i: B-cell lymphoma 2 inhibitor, BETi: bromodomain and extra-terminal protein inhibitor, P-TEFb: positive transcription elongation factor b, LTR: HIV long terminal repeat promoter, Ac: acetylation, Me: methylation.

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Table 1

Cancer therapies investigated in HIV

Drug class	Promising compounds in HIV research	Clinical development phase in oncology	Proposed effect in HIV infection	Clinical studies in HIV
i. Latency reversing agents				
HDAC inhibitors	Vorinostat, romidepsin, panobinostat	Licensed (CTCL, MM)	Reversing HIV latency by chromatin remodeling	Yes, refs 9, 10, 11, 12, 13
BET inhibitors	OTX015, JQ1	Phase I/II	Reversing HIV latency by promoting recruitment of P-TEFb to the HIV LTR	No
Histone methyltransferase inhibitors	Low doses only of chaetocin, BIX-01294 or DNZep	Not safe at doses tested / Pre-clinical	Prevents histone 3 methylation that represses HIV transcription, thereby reactivating latent HIV	No
DNA methyltransferase inhibitors	Azacitidine, decitabine	Licensed (MDS)	Prevents CpG methylation at the HIV promoter that represses HIV transcription	No
PKC agonists	Bryostatins-1, prostratin	Phase I/II	Reversing HIV latency by activating NF- κ B signalling pathways	Yes, ref 17
ii. Apoptosis promoting compounds				
Bcl-2 antagonists	Venetoclax	Licensed (CLL), Phase I-III	Inhibits anti-apoptotic BCL-2, sensitizing cells to apoptosis. When combined with LRA reactivation, leads to preferential apoptosis of HIV infected cells	No
RIG-I inducers	Acitretin	Licensed (psoriasis only)	Reactivates HIV transcription	No

Drug class	Promising compounds in HIV research	Clinical development phase in oncology	Proposed effect in HIV infection	Clinical studies in HIV
PI3k/Akt inhibitors	Perifosine, arctigenin	Phase I/II	and activates RIG-I induced apoptosis, leading to selective apoptosis of HIV infected cells Blocks PI3K/Akt pathway signalling, sensitizing HIV-infected cells for apoptosis	No
SMAC mimetics	Birinipant, SBI-0637142, LCL161	Phase I/II	Inhibits inhibitor of apoptosis proteins (IAPs), sensitizing HIV infected cells for apoptosis, induces viral replication	No
Tyrosine kinase inhibitors	Ibrutinib	Licensed	Impairs Bruton's tyrosine kinase on the surface of HIV-infected cells, inducing selective depletion of HIV-infected cells	No
iii. Immune modulation				
Immune checkpoint inhibitors	Ipilimumab, pembrolizumab, nivolumab	Licensed (melanoma, NSCLC)	Enhancing HIV-specific T cell responses; reversing HIV latency	Yes, refs 60
TLR agonists	GS-9620, MGN1703	Phase I, II	Activating DCs and NK cells; reversing HIV latency	Yes, refs 76, 78

HDAC: histone deacetylase, CTCL: cutaneous T cell lymphoma, MM: multiple myeloma, BET: bromodomain and extra terminal, P-TEFb: positive transcription elongation factor b, MDS: myelodysplastic syndrome, PKC: protein kinase C, CLL: chronic lymphocytic leukemia, LRA: latency reversing agent, RIG-I: retinoic acid-inducible gene I, PI3k: phosphoinositide 3-kinase, SMAC: second mitochondria-derived activator of caspase, NSCLC: non-small cell lung cancer, DC: dendritic cell, NK: natural killer.