REVIEW

Targeting the latent reservoir to achieve functional HIV cure

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Abstract

While highly active anti-retroviral therapy has greatly improved the lives of HIV-infected individuals, current treatments are unable to completely eradicate the virus. This is due to the presence of HIV latently infected cells which harbor transcriptionally silent HIV. Latent HIV does not replicate or produce viral proteins, thereby preventing efficient targeting by anti-retroviral drugs. Strategies to target the HIV latent reservoir include viral reactivation, enhancing host defense mechanisms, keeping latent HIV silent, and using gene therapy techniques to knock out or reactivate latent HIV. While research into each of these areas has yielded promising results, currently no one mechanism eradicates latent HIV. Instead, combinations of these approaches should be considered for a potential HIV functional cure.

Keywords

HIV, latent HIV, targeting latent HIV, viral reactivation, host defense mechanisms, gene therapy

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Introduction

In the twenty years since the implementation of highly active anti-retroviral therapy (HAART), the overall face of HIV as a global health issue has changed¹. HAART—composed of a cocktail of anti-retroviral drugs which target proteins expressed at different steps in the HIV replication cycle—can affect only cells that harbor actively replicating virus. HIV+ individuals are able to live fairly normal lives on maintenance HAART, with minimal side effects. Nevertheless, the effects of HIV infection continue to be evident in these suppressed individuals, who continue to suffer from a number of metabolic, immunologic, and neurologic co-morbidities². Thus, despite reducing plasma viremia below detection limits, the virus is not eliminated. There is evidence that low levels of replication occur in suppressed individuals, primarily in tissue reservoirs; however, this is not reflected in systemic plasma viremia in these individuals^{3,4}. HAART requires life-long administration. Following even brief treatment interruption, HIV rebounds rapidly from its reservoirs^{5–7}. Goals of the present research are to eliminate, suppress permanently, or render cells inhospitable to the hidden HIV in infected individuals.

Research efforts to understand and target HIV reservoirs have focused on four main categories outlined in this review (Figure 1): first, reactivation of latent HIV by capitalizing on the ability of host cellular activation signals and transcription factors (TFs) to ‘shock’ the virus out of hiding; second, killing of reactivated HIV by strengthening the immune system, which has been crippled

by the infection; third, keeping latent reservoirs permanently suppressed; and, finally, targeting HIV and CD4+ T cells, which are the primary host cells for the virus, via new gene therapy approaches.

Shock

Chronic infection by HIV is characterized by severe depletion of CD4+ T cells and continuing inflammation, which contribute to HIV-associated co-morbidities². Continued exposure to inflammatory cytokines exhausts the immune system. It also elevates the expression of the receptors programmed death 1 (PD-1)⁸ and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4)⁹ on T cells. Blockade of these molecules is used as a treatment for solid tumors¹⁰ and could reinvigorate exhausted T cells in HIV+ patients¹¹. These individuals also produce elevated levels of inhibitory cytokines interleukin (IL)-10 and transforming growth factor-β (TGF-β)^{12,13}. Indeed, blocking IL-10 results in increased T cell activity in a hepatitis C infection model^{14,15}.

Growth factor therapy, including treatment with IL-2, -7, or -15, is being explored as a means to stimulate T cell recovery. IL-2 and IL-7 are important T cell growth and proliferation factors. Infusion with IL-2 and IL-7 results in enhanced T cell production and memory T cell proliferation^{16–18}. IL-15 enhances cytotoxic CD8+ T lymphocyte (CTL) and natural killer (NK) cell activity *in vitro*. Indeed, the IL-15 super-agonist ALT-803 is currently in preclinical trials¹⁹.

Figure 1. Four main approaches that target the latent reservoir of HIV. Four research areas, which reactivate HIV (1. shock), eliminate HIV (2. kill), silence HIV (3. silence), or alter the immune system to resist HIV (4. gene therapy) should contribute to the functional or complete cure of HIV in infected individuals. Within each area are individual components of that therapy. They can be applied individually or in combinations, which should decrease their doses and deleterious effects. Most likely, there will be additional approaches in the future.

Latent HIV is primarily found in resting CD4+ T cells in the periphery. Resting cells have low levels of cellular TFs, which are also required for HIV replication, including NF- κ B, P-TEFb, and CDK11^{20,21}. Among the first examined latency reversing agents (LRAs) were histone deacetylase inhibitors (HDACis) and BET bromodomain inhibitors (BETis), which induce chromatin stress and induce the release of positive transcription elongation factor b (P-TEFb) from its repressive complex²². HDACis—such as panobinostat²³, romidepsin²⁴, SAHA²⁵, and valproic acid²⁶—and BETis—such as JQ1²⁷—all reactivate HIV in cell line models of latency. However, they do not work in human primary resting infected T cells^{28,29} because they contain very low levels of necessary TFs^{20,21}. Thus, clinical trials with SAHA resulted in only a modest and transient reactivation of HIV³⁰, making it an impractical mono-therapy for HIV reactivation.

Since HDACis and BETis do not increase levels of required TFs, some activation of CD4+ T cells is required. Indeed, protein kinase C (PKC) agonists, such as prostratin³¹ and bryostatin³², and the MAPK agonist procyanidin^{33,34} can reactivate HIV in cell line models and primary CD4+ T cells. However, prostratin is toxic at therapeutic levels, leading to muscle pain, respiratory distress, and hypertension. Bryostatin, derived from a marine animal, *Bugula neritina*, not only has similar side effects but is also cost prohibitive to manufacture. Because of these limitations, a number of synthetic analogues of prostratin and bryostatin with reduced toxicity *in vitro* are being developed^{35–37}. Ingenols, which are purified from Euphorbia plants, represent additional PKC agonists of interest. Native and chemically modified ingenols reactivate HIV in cell lines and primary T cells^{38–40}. These PKC agonists also increase cellular levels of necessary TFs³⁸. Thus, select MAPK and PKC agonists represent attractive candidates to reactivate latent HIV.

Combining several of these approaches has the greatest potential to purge the viral reservoir. Indeed, lower doses of a T cell activator and an LRA (HDACi or BETi) can be administered for increased potency and reduced pro-inflammatory responses^{41–43}. Further understanding of HIV integration, transcription, and reactivation, as well as host cell behaviors, will inform optimal combinations of activators and LRAs.

Kill

Strategies to remove HIV by enhancing the killing by CTL and NK cells⁴⁴ or via broadly neutralizing antibodies (bNAbs) represent the second major field of research in HIV eradication. It is also important to investigate kill strategies in the context of the aforementioned shock therapies because many of the treatments proposed to reactivate latent HIV also dampen CTL function⁴⁵, which is already impaired in HIV+ individuals¹¹.

Using modified cytomegalovirus (CMV), a live vaccine expressing several simian immunodeficiency virus (SIV) antigens, was found to protect rhesus macaques against viral challenge^{46–48}. Vaccinated animals initially appeared to be infected; however, they gained protection against SIV and showed enhanced effector T cell function against viral antigens.

Another approach involves bNAbs⁴⁹. Following infection, anti-HIV antibodies are abundant in HIV+ patients; however, owing to the ability of the virus to mutate, the majority of them fail to eliminate the virus. bNAbs are the exception, in that they recognize many clades of HIV as well as escape mutants of the virus. In several studies, they not only neutralized virions released from activated CD4+ T cells from patients⁵⁰ but also reduced the viral rebound following HIV reactivation in a humanized mouse model⁵¹. However, even the most potent bNAbs are each only effective against a narrow subset of HIV clinical isolates, suggesting that effective bNAb approaches may require a combination of several bNAbs⁵². A second antibody approach utilizes bispecific antibodies, wherein one arm of the Fab portion of the antibody recognizes HIV envelope and the second arm recognizes CD3, making the cell vulnerable to CTL-mediated killing.

Finally, in an effort to achieve more effective killing, chimeric antigen receptors (CARs), which increase T cell receptor avidity and activation, are being explored. They can be engineered to recognize specific viral proteins; CARs against CD19, which is a B cell receptor, led to an astounding 90% remission rate in acute leukemia^{53,54}. However, one caveat to CARs is that these cells are long-lived and can have substantial off-target effects.

Silence

The success of HAART has demonstrated that keeping the virus suppressed results in markedly healthier individuals. Resting infected cells do not produce HIV. Thus, these strategies rely on reducing T cell activation, which should also reduce the HIV-associated inflammation found in chronically infected individuals². JAK and STAT molecules are important signaling molecules associated with many cytokine receptors. Ruxolitinib and tofacitinib, two JAK inhibitors that are approved for the treatment of rheumatoid arthritis and myelofibrosis, were tested against HIV, HIV2, and simian HIV (SHIV). They inhibited HIV reactivation⁵⁵, and, furthermore, ruxolitinib attenuated encephalitis symptoms in infected humanized mice⁵⁶. Cyclosporine A, an immunosuppressant used primarily to prevent transplant rejection⁵⁷, inhibits T cell proliferation by blocking IL-2 signaling in T cells⁵⁸. Infected patients treated with cyclosporine A had some T cell recovery⁵⁹ but limited suppression of HIV replication^{60,61}.

The inhibitor didehydro-cortistatin A (dCA) acts via a suppressive mechanism that primarily targets HIV transcription. dCA binds to the basic domain in the HIV regulatory protein Tat, inhibits its interactions with the RNA response element TAR, and prevents its activation of HIV transcription⁶². dCA inhibits HIV reactivation in cell lines, primary cells, and peripheral blood mononuclear cells (PBMCs) from HAART-suppressed patients⁶². Furthermore, dCA may also contribute to continued HIV suppression by inhibiting inflammatory cytokine expression⁶³.

Gene therapy

Recently, a number of groups have taken advantage of cutting edge gene therapy approaches to HIV cure. However, as with any gene therapy approach, the barriers include delivery, specificity, off-target effects, costs, and ethical concerns.

The single case of successful HIV cure was achieved by the reconstitution of the patient's immune system with donor bone marrow containing a natural mutation in the CCR5 HIV co-receptor⁶⁴. This patient was treated for acute leukemia with several courses of total lymphoid irradiation followed by two separate bone marrow transplantations. Attempts to replicate this therapy used the Zn++ finger nuclease⁶⁵ and more recently CRISPR/Cas9 targeting of CCR5 to induce the delta 32 mutation in patients' own hematopoietic cells^{66,67}, which were then returned to the host. Since only mature cells were used, the effects of these manipulated cells were not permanent⁶⁵. Recent work using CRISPR/Cas9 to target the second HIV co-receptor, CXCR4, has also yielded promising results^{68,69}.

While HIV and SIV are highly related viruses, HIV cannot infect non-human primates, as their restriction factors block HIV infection more effectively than their human counterparts⁷⁰. Therefore, altering human restriction factors to behave like their simian counterparts represents an attractive strategy. One such factor is TRIM5. Of special interest is TRIM5 from owl monkeys, which is linked in frame to cyclophilin A, and this fusion protein blocks HIV⁷¹. Using lentiviral vectors to deliver Trim-Cyp has blocked HIV effectively in cell lines and primary T cells⁷². Additionally, it has been used successfully in a triple combination anti-HIV lentiviral vector approach in an infected humanized mouse model⁷³.

Recently, CRISPR/Cas9 technology has emerged as the most versatile and effective gene therapy approach. Using a DNA targeting strategy utilized by bacterial CRISPR, any number of specific guide RNAs can be loaded into the Cas9 protein to target specific areas of DNA for knock out or knock in of genes⁷⁴. Similarly, this technology has been used to knock out and reactivate latent HIV. Targeting various regions of the HIV LTR inactivated the virus in infected cell lines⁷⁵ and prevented their reinfection⁷⁶. However, viral target sequences can mutate, and HIV LTR-specific guide RNA can fail to recognize and target the mutant sequences, preventing long-term eradication by this method⁷⁷. To reactivate HIV, a defective Cas9 protein (dCas9) is used, which is fused to four copies of the herpes simplex VP16 activation domain (VP64) or a synergistic activation mediator (SAM) complex. Again, guide RNAs bring these dCas9

activators to the initiated transcription machinery. This targeting results in potent reactivation in latently infected cell lines^{78–80}.

Summary

Although HIV infection in the era of HAART has become a manageable chronic infection, problems with adherence to drug regimen, co-morbidities, and the emergence of drug resistance emphasize the need for continued research into HIV cure. Since the barrier to cure is the HIV reservoir, targeting this persistent virus is critical. The approaches detailed in this review represent a spectrum of the current research: however, eliminating the remaining 10⁶ to 10⁸ latently infected cells⁸¹ will require a combination of approaches. Mechanisms, such as HIV reactivation, will reveal hidden virus. However, the severely crippled immune system and further decreased CTL function indicate that it must be paired with the boosting of anti-viral host defenses. Likewise, keeping latent HIV in a suppressed state could keep HIV+ patients relatively healthy but less able to resist other infections and/or cancer. Using gene therapy to create a parallel immune system, where cells resist HIV infection, could complement all other approaches but is not scalable or affordable in resource-poor countries. While none of these approaches represent the eradication of HIV, combining several treatment modalities could bring us closer to a functional cure, where prolonged HAART-free and disease-free intervals would be achieved in infected patients.

Competing interests

The authors declare that they have no competing interests.

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References

- UNAIDS: **AIDS by the numbers 2015**. Joint United Nations Programme on HIV/AIDS (UNAIDS). 2015.
[Reference Source](#)
- Marin B, Thiébaud R, Bucher HC, *et al.*: **Non-AIDS-defining deaths and immunodeficiency in the era of combination antiretroviral therapy**. *AIDS*. 2009; 23(13): 1743–53.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Buzón MJ, Massanella M, Llibre JM, *et al.*: **HIV-1 replication and immune dynamics are affected by raltegravir intensification of HAART-suppressed subjects**. *Nat Med*. 2010; 16(4): 460–5.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Lorenzo-Redondo R, Fryer HR, Bedford T, *et al.*: **Persistent HIV-1 replication maintains the tissue reservoir during therapy**. *Nature*. 2016; 530(7588): 51–6.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | **F1000 Recommendation**
- Chun TW, Stuyver L, Mizell SB, *et al.*: **Presence of an inducible HIV-1 latent reservoir during highly active antiretroviral therapy**. *Proc Natl Acad Sci U S A*. 1997; 94(24): 13193–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Finzi D, Hermankova M, Pierson T, *et al.*: **Identification of a reservoir for HIV-1 in patients on highly active antiretroviral therapy**. *Science*. 1997; 278(5341): 1295–300.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Wong JK, Hezareh M, Günthard HF, *et al.*: **Recovery of replication-competent HIV despite prolonged suppression of plasma viremia**. *Science*. 1997; 278(5341): 1291–5.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Day CL, Kaufmann DE, Kiepiela P, *et al.*: **PD-1 expression on HIV-specific T cells is associated with T-cell exhaustion and disease progression**. *Nature*. 2006; 443(7109): 350–4.
[PubMed Abstract](#) | [Publisher Full Text](#) | **F1000 Recommendation**

9. **F** Kaufmann DE, Kavanagh DG, Pereyra F, *et al.*: **Upregulation of CTLA-4 by HIV-specific CD4⁺ T cells correlates with disease progression and defines a reversible immune dysfunction.** *Nat Immunol.* 2007; 8(11): 1246–54.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
10. **F** Callahan MK, Wolchok JD: **At the bedside: CTLA-4- and PD-1-blocking antibodies in cancer immunotherapy.** *J Leukoc Biol.* 2013; 94(1): 41–53.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
11. **F** Jones RB, Walker BD: **HIV-specific CD8⁺ T cells and HIV eradication.** *J Clin Invest.* 2016; 126(2): 455–63.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
12. Renga B, Francisci D, D'Amore C, *et al.*: **HIV-1 infection is associated with changes in nuclear receptor transcriptome, pro-inflammatory and lipid profile of monocytes.** *BMC Infect Dis.* 2012; 12: 274.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
13. Yadav A, Collman RG: **CNS inflammation and macrophage/microglial biology associated with HIV-1 infection.** *J Neuroimmune Pharmacol.* 2009; 4(4): 430–47.
[PubMed Abstract](#) | [Publisher Full Text](#)
14. Brooks DG, Ha SJ, Elsaesser H, *et al.*: **IL-10 and PD-L1 operate through distinct pathways to suppress T-cell activity during persistent viral infection.** *Proc Natl Acad Sci U S A.* 2008; 105(51): 20428–33.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
15. Rigopoulou EI, Abbott WG, Haigh P, *et al.*: **Blocking of interleukin-10 receptor—a novel approach to stimulate T-helper cell type 1 responses to hepatitis C virus.** *Clin Immunol.* 2005; 117(1): 57–64.
[PubMed Abstract](#) | [Publisher Full Text](#)
16. Levy Y, Lacabaratz C, Weiss L, *et al.*: **Enhanced T cell recovery in HIV-1-infected adults through IL-7 treatment.** *J Clin Invest.* 2009; 119(4): 997–1007.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
17. Scripture-Adams DD, Brooks DG, Korin YD, *et al.*: **Interleukin-7 induces expression of latent human immunodeficiency virus type 1 with minimal effects on T-cell phenotype.** *J Virol.* 2002; 76(24): 13077–82.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
18. **F** Lévy Y, Sereti I, Tambussi G, *et al.*: **Effects of recombinant human interleukin 7 on T-cell recovery and thymic output in HIV-infected patients receiving antiretroviral therapy: results of a phase I/IIa randomized, placebo-controlled, multicenter study.** *Clin Infect Dis.* 2012; 55(2): 291–300.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
19. **F** Seay K, Church C, Zheng JH, *et al.*: **In Vivo Activation of Human NK Cells by Treatment with an Interleukin-15 Superagonist Potently Inhibits Acute In Vivo HIV-1 Infection in Humanized Mice.** *J Virol.* 2015; 89(12): 6264–74.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
20. Bartholomeeusen K, Xiang Y, Fujinaga K, *et al.*: **Bromodomain and extra-terminal (BET) bromodomain inhibition activate transcription via transient release of positive transcription elongation factor b (P-TEFb) from TSK small nuclear ribonucleoprotein.** *J Biol Chem.* 2012; 287(43): 36609–16.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
21. Yu W, Ramakrishnan R, Wang Y, *et al.*: **Cyclin T1-dependent genes in activated CD4⁺ T and macrophage cell lines appear enriched in HIV-1 co-factors.** *PLoS One.* 2008; 3(9): e3146.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
22. Bartholomeeusen K, Fujinaga K, Xiang Y, *et al.*: **Histone deacetylase inhibitors (HDACis) that release the positive transcription elongation factor b (P-TEFb) from its inhibitory complex also activate HIV transcription.** *J Biol Chem.* 2013; 288(20): 14400–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
23. Rasmussen TA, Schmeltz Sogaard O, Brinkmann C, *et al.*: **Comparison of HDAC inhibitors in clinical development: effect on HIV production in latently infected cells and T-cell activation.** *Hum Vaccin Immunother.* 2013; 9(5): 993–1001.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
24. **F** Wei DG, Chiang V, Fyne E, *et al.*: **Histone deacetylase inhibitor romidepsin induces HIV expression in CD4⁺ T cells from patients on suppressive antiretroviral therapy at concentrations achieved by clinical dosing.** *PLoS Pathog.* 2014; 10(4): e1004071.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
25. Contreras X, Schwenecker M, Chen CS, *et al.*: **Suberoylanilide hydroxamic acid reactivates HIV from latently infected cells.** *J Biol Chem.* 2009; 284(11): 6782–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
26. Routy JP, Tremblay CL, Angel JB, *et al.*: **Valproic acid in association with highly active antiretroviral therapy for reducing systemic HIV-1 reservoirs: results from a multicentre randomized clinical study.** *HIV Med.* 2012; 13(5): 291–6.
[PubMed Abstract](#) | [Publisher Full Text](#)
27. Boehm D, Calvanese V, Dar RD, *et al.*: **BET bromodomain-targeting compounds reactivate HIV from latency via a Tat-independent mechanism.** *Cell Cycle.* 2013; 12(3): 452–62.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
28. Spina CA, Anderson J, Archin NM, *et al.*: **An in-depth comparison of latent HIV-1 reactivation in multiple cell model systems and resting CD4⁺ T cells from aviremic patients.** *PLoS Pathog.* 2013; 9(12): e1003834.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
29. Blazkova J, Chun TW, Belay BW, *et al.*: **Effect of histone deacetylase inhibitors on HIV production in latently infected, resting CD4⁺ T cells from infected individuals receiving effective antiretroviral therapy.** *J Infect Dis.* 2012; 206(5): 765–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
30. **F** Archin NM, Liberty AL, Kashuba AD, *et al.*: **Administration of vorinostat disrupts HIV-1 latency in patients on antiretroviral therapy.** *Nature.* 2012; 487(7408): 482–5.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
31. Korin YD, Brooks DG, Brown S, *et al.*: **Effects of prostratin on T-cell activation and human immunodeficiency virus latency.** *J Virol.* 2002; 76(16): 8118–23.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
32. Pérez M, de Vinuesa AG, Sanchez-Duffhues G, *et al.*: **Bryostatins synergize with histone deacetylase inhibitors to reactivate HIV-1 from latency.** *Curr HIV Res.* 2010; 8(6): 418–29.
[PubMed Abstract](#) | [Publisher Full Text](#)
33. **F** Hori T, Bamor J, Huu TN, *et al.*: **Procyanidin trimer C1 derived from Theobroma cacao reactivates latent human immunodeficiency virus type 1 provirus.** *Biochem Biophys Res Commun.* 2015; 459(2): 288–93.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
34. **F** Wang C, Yang S, Lu H, *et al.*: **A Natural Product from Polygonum cuspidatum Sieb. Et Zucc. Promotes Tat-Dependent HIV Latency Reversal through Triggering P-TEFb's Release from 7SK snRNP.** *PLoS One.* 2015; 10(11): e0142739.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
35. Beans EJ, Fournogarakis D, Gauntlett C, *et al.*: **Highly potent, synthetically accessible prostratin analogs induce latent HIV expression in vitro and ex vivo.** *Proc Natl Acad Sci U S A.* 2013; 110(29): 11698–703.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
36. **F** DeChristopher BA, Loy BA, Marsden MD, *et al.*: **Designed, synthetically accessible bryostatins analogues potentially induce activation of latent HIV reservoirs in vitro.** *Nat Chem.* 2012; 4(9): 705–10.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
37. **F** Wender PA, Nakagawa Y, Near KE, *et al.*: **Computer-guided design, synthesis, and protein kinase C affinity of a new salicylate-based class of bryostatins analogs.** *Org Lett.* 2014; 16(19): 5136–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
38. Pandeló José D, Bartholomeeusen K, da Cunha RD, *et al.*: **Reactivation of latent HIV-1 by new semi-synthetic ingenol esters.** *Virology.* 2014; 462–463: 328–39.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
39. **F** Jiang G, Mendes EA, Kaiser P, *et al.*: **Reactivation of HIV latency by a newly modified ingenol derivative via protein kinase C- α -NF- κ B signaling.** *AIDS.* 2014; 28(11): 1555–66.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
40. **F** Abreu CM, Price SL, Shirk EN, *et al.*: **Dual role of novel ingenol derivatives from Euphorbia tirucalli in HIV replication: inhibition of de novo infection and activation of viral LTR.** *PLoS One.* 2014; 9(5): e97257.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
41. **F** Jiang G, Mendes EA, Kaiser P, *et al.*: **Synergistic Reactivation of Latent HIV Expression by Ingenol-3-Angelate, PEP005, Targeted NF- κ B Signaling in Combination with JQ1 Induced p-TEFb Activation.** *PLoS Pathog.* 2015; 11(7): e1005066.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
42. Darcis G, Kula A, Bouchat S, *et al.*: **An In-Depth Comparison of Latency-Reversing Agent Combinations in Various In Vitro and Ex Vivo HIV-1 Latency Models Identified Bryostatins-1+JQ1 and Ingenol-B+JQ1 to Potently Reactivate Viral Gene Expression.** *PLoS Pathog.* 2015; 11(7): e1005063.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
43. **F** Laird GM, Bullen CK, Rosenbloom DI, *et al.*: **Ex vivo analysis identifies effective HIV-1 latency-reversing drug combinations.** *J Clin Invest.* 2015; 125(5): 1901–12.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
44. Scully E, Alter G: **NK Cells in HIV Disease.** *Curr HIV/AIDS Rep.* 2016; 13(2): 85–94.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
45. **F** Jones RB, O'Connor R, Mueller S, *et al.*: **Histone deacetylase inhibitors impair the elimination of HIV-infected cells by cytotoxic T-lymphocytes.** *PLoS Pathog.* 2014; 10(8): e1004287.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
46. Cicin-Sain L, Sylwester AW, Hagen SI, *et al.*: **Cytomegalovirus-specific T cell immunity is maintained in immunosenescent rhesus macaques.** *J Immunol.* 2011; 187(4): 1722–32.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
47. **F** Hansen SG, Ford JC, Lewis MS, *et al.*: **Profound early control of highly pathogenic SIV by an effector memory T-cell vaccine.** *Nature.* 2011; 473(7348): 523–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
48. **F** Hansen SG, Sacha JB, Hughes CM, *et al.*: **Cytomegalovirus vectors violate CD8⁺ T cell epitope recognition paradigms.** *Science.* 2013; 340(6135): 1237874.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
49. Halper-Stromberg A, Nussenzweig MC: **Towards HIV-1 remission: potential roles for broadly neutralizing antibodies.** *J Clin Invest.* 2016; 126(2): 415–23.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

50. **F** Chun TW, Murray D, Justement JS, *et al.*: **Broadly neutralizing antibodies suppress HIV in the persistent viral reservoir.** *Proc Natl Acad Sci U S A.* 2014; 111(36): 13151–6.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
51. **F** Halper-Stromberg A, Lu CL, Klein F, *et al.*: **Broadly neutralizing antibodies and viral inducers decrease rebound from HIV-1 latent reservoirs in humanized mice.** *Cell.* 2014; 158(5): 989–99.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
52. **F** Bruel T, Guivel-Benhassine F, Amraoui S, *et al.*: **Elimination of HIV-1-infected cells by broadly neutralizing antibodies.** *Nat Commun.* 2016; 7: 10844.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
53. Grupp SA, Kalos M, Barrett D, *et al.*: **Chimeric antigen receptor-modified T cells for acute lymphoid leukemia.** *N Engl J Med.* 2013; 368(16): 1509–18.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
54. **F** Maude SL, Frey N, Shaw PA, *et al.*: **Chimeric antigen receptor T cells for sustained remissions in leukemia.** *N Engl J Med.* 2014; 371(16): 1507–17.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
55. **F** Gavegnano C, Deterio M, Montero C, *et al.*: **Ruxolitinib and tofacitinib are potent and selective inhibitors of HIV-1 replication and virus reactivation in vitro.** *Antimicrob Agents Chemother.* 2014; 58(4): 1977–86.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
56. **F** Haile WB, Gavegnano C, Tao S, *et al.*: **The Janus kinase inhibitor ruxolitinib reduces HIV replication in human macrophages and ameliorates HIV encephalitis in a murine model.** *Neurobiol Dis.* 2016; pii: S0969-9961(16)30028-6.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
57. Starzl TE, Weil R 3rd, Iwatsuki S, *et al.*: **The use of cyclosporin A and prednisone in cadaver kidney transplantation.** *Surg Gynecol Obstet.* 1980; 151(1): 17–26.
[PubMed Abstract](#) | [Free Full Text](#)
58. Bunjes D, Hardt C, Rölinghoff M, *et al.*: **Cyclosporin A mediates immunosuppression of primary cytotoxic T cell responses by impairing the release of interleukin 1 and interleukin 2.** *Eur J Immunol.* 1981; 11(8): 657–61.
[PubMed Abstract](#) | [Publisher Full Text](#)
59. Andrieu JM, Even P, Venet A, *et al.*: **Effects of cyclosporin on T-cell subsets in human immunodeficiency virus disease.** *Clin Immunol Immunopathol.* 1988; 47(2): 181–98.
[PubMed Abstract](#) | [Publisher Full Text](#)
60. Markowitz M, Vaida F, Hare CB, *et al.*: **The virologic and immunologic effects of cyclosporine as an adjunct to antiretroviral therapy in patients treated during acute and early HIV-1 infection.** *J Infect Dis.* 2010; 201(9): 1298–302.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
61. Rizzardi GP, Harari A, Capiluppi B, *et al.*: **Treatment of primary HIV-1 infection with cyclosporin A coupled with highly active antiretroviral therapy.** *J Clin Invest.* 2002; 109(5): 681–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
62. Mousseau G, Kessing CF, Fromentin R, *et al.*: **The Tat Inhibitor Didehydro-Cortistatin A Prevents HIV-1 Reactivation from Latency.** *MBio.* 2015; 6(4): e00465.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
63. **F** Mediouni S, Jablonski J, Paris JJ, *et al.*: **Didehydro-cortistatin A inhibits HIV-1 Tat mediated neuroinflammation and prevents potentiation of cocaine reward in Tat transgenic mice.** *Curr HIV Res.* 2015; 13(1): 64–79.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
64. **F** Hütter G, Nowak D, Mossner M, *et al.*: **Long-term control of HIV by CCR5 Delta32/Delta32 stem-cell transplantation.** *N Engl J Med.* 2009; 360(7): 692–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
65. **F** Tebas P, Stein D, Tang WW, *et al.*: **Gene editing of CCR5 in autologous CD4 T cells of persons infected with HIV.** *N Engl J Med.* 2014; 370(10): 901–10.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
66. **F** Ye L, Wang J, Beyer AI, *et al.*: **Seamless modification of wild-type induced pluripotent stem cells to the natural CCR5Δ32 mutation confers resistance to HIV infection.** *Proc Natl Acad Sci U S A.* 2014; 111(26): 9591–6.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
67. **F** Wang W, Ye C, Liu J, *et al.*: **CCR5 gene disruption via lentiviral vectors expressing Cas9 and single guided RNA renders cells resistant to HIV-1 infection.** *PLoS One.* 2014; 9(12): e115987.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
68. **F** Schumann K, Lin S, Boyer E, *et al.*: **Generation of knock-in primary human T cells using Cas9 ribonucleoproteins.** *Proc Natl Acad Sci U S A.* 2015; 112(33): 10437–42.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
69. **F** Hou P, Chen S, Wang S, *et al.*: **Genome editing of CXCR4 by CRISPR/cas9 confers cells resistant to HIV-1 infection.** *Sci Rep.* 2015; 5: 15577.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
70. Chan E, Towers GJ, Qasim W: **Gene therapy strategies to exploit TRIM derived restriction factors against HIV-1.** *Viruses.* 2014; 6(1): 243–63.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
71. Carthagen L, Parise MC, Ringeard M, *et al.*: **Implication of TRIM alpha and TRIMCyp in interferon-induced anti-retroviral restriction activities.** *Retrovirology.* 2008; 5: 59.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
72. Neagu MR, Ziegler P, Pertel T, *et al.*: **Potent inhibition of HIV-1 by TRIM5-cyclophilin fusion proteins engineered from human components.** *J Clin Invest.* 2009; 119(10): 3035–47.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
73. Walker JE, Chen RX, McGee J, *et al.*: **Generation of an HIV-1-resistant immune system with CD34⁺ hematopoietic stem cells transduced with a triple-combination anti-HIV lentiviral vector.** *J Virol.* 2012; 86(10): 5719–29.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
74. Wright AV, Nuñez JK, Doudna JA: **Biology and Applications of CRISPR Systems: Harnessing Nature's Toolbox for Genome Engineering.** *Cell.* 2016; 164(1–2): 29–44.
[PubMed Abstract](#) | [Publisher Full Text](#)
75. Ebina H, Misawa N, Kanemura Y, *et al.*: **Harnessing the CRISPR/Cas9 system to disrupt latent HIV-1 provirus.** *Sci Rep.* 2013; 3: 2510.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
76. **F** Hu W, Kaminski R, Yang F, *et al.*: **RNA-directed gene editing specifically eradicates latent and prevents new HIV-1 infection.** *Proc Natl Acad Sci U S A.* 2014; 111(31): 11461–6.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
77. **F** Wang G, Zhao N, Berkhout B, *et al.*: **CRISPR-Cas9 Can Inhibit HIV-1 Replication but NHEJ Repair Facilitates Virus Escape.** *Mol Ther.* 2016; 24(3): 522–6.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
78. **F** Zhang Y, Yin C, Zhang T, *et al.*: **CRISPR/gRNA-directed synergistic activation mediator (SAM) induces specific, persistent and robust reactivation of the HIV-1 latent reservoirs.** *Sci Rep.* 2015; 5: 16277.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
79. **F** Saayman SM, Lazar DC, Scott TA, *et al.*: **Potent and Targeted Activation of Latent HIV-1 Using the CRISPR/dCas9 Activator Complex.** *Mol Ther.* 2016; 24(3): 488–98.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
80. **F** Limsirichai P, Gaj T, Schaffer DV: **CRISPR-mediated Activation of Latent HIV-1 Expression.** *Mol Ther.* 2016; 24(3): 499–507.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
81. Massanella M, Richman DD: **Measuring the latent reservoir in vivo.** *J Clin Invest.* 2016; 126(2): 464–72.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

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