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Retinoids: novel potential therapeutics in the pursuit of HIV-1 cure

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Human immunodeficiency virus (HIV) infection remains a global epidemic. While antiretroviral therapy (ART) suppresses viral replication, cessation of ART results in viral rebound necessitating lifelong treatment. This is a result of a reservoir of latently infected cells, resistant to clearance by ART and the major obstacle in curing HIV. HIV cure strategies have focused on reactivating this latent reservoir with latency reversal agents (LRAs) along with enhancement of anti-HIV immunity to eliminate reactivated HIV. Retinoic acid (RA) derivatives are promising therapeutics that may promote clearance HIV latent reservoir allowing for definitive cure. In addition to plausible mechanisms for depleting the latent reservoir with LRA activity *via* the p300 acetyl transferase pathway, countering HIV-mediated suppression of RIG-I and IRF-3, and proposed induction of selective apoptosis of HIV-infected cells *via* RIG-I, RA may also limit HIV spread by augmenting cellular trafficking *via* CCR7 and CCR9 and induce accumulation of high-affinity effector CD8+ T cells that aid immune clearance of HIV-infected cells. Furthermore, due to their specificity for HIV-infected cells, retinoids are attractive agents to form the basis of multidrug regimens. Altogether, retinoids have many compelling properties as potential novel therapeutics in the cure of HIV.

KEYWORDS

HIV - human immunodeficiency virus, retinoid acid, CD4, antiviral, apoptosis

Human immunodeficiency virus and antiretroviral therapy

Since the early 1980s, more than 35 million people have died of HIV or acquired immune deficiency syndrome. The World Health Organization estimates 37.7 million people currently living with HIV, with 1.5 million more infected last year (1). After the advent of effective antiretroviral therapy (ART) in the mid-1990s, HIV was transformed

from a near universally fatal disease to a chronic one requiring life-long therapy to maintain health and prevent transmission. Despite its effectiveness in suppressing viral replication, ART does not eradicate HIV infection. Additionally, initiation and maintenance of lifelong ART remains a global challenge due to cost, stigma, and other important barriers to access. These limitations have spurred considerable effort in finding a cure.

Curing HIV requires eradication of the reservoir of HIV-infected cells that persist during ART (2). One cure strategy is the "Shock and Kill" approach, where active replication of HIV is induced in latently infected cells (i.e. reversing latency), making them more susceptible to immune-mediated clearance, ART-mediated clearance, or apoptotic pathways. Other cure strategies include: 1) "Block and Lock", using latency promoting agents (LPAs) to drive HIV-infected cells into deeper latency to permanently suppresses viral transcription (3), 2) Introduction of an HIV-resistant T cell population *via* hematopoietic stem cell transplant (4), and 3) Immunotherapy including immune checkpoint inhibitors (5), Toll-like receptor agonists (6), and broadly neutralizing antibodies (7).

The "Shock and Kill" approach requires two steps: 1) "Shock" or latency reversal *via* aptly named Latency Reversal Agents (LRAs), and 2) "Kill" or clearance of the reactivated HIV-infected cells. Many potentially useful drug classes have been identified as LRAs (3, 8–10), but there has been limited success in delivering the subsequent kill. One novel class that may possess both "Shock" and "Kill" activities are retinoids, derivatives of Vitamin A which perform important roles in immune homeostasis and modulation affecting T cell signaling, homing, and differentiation. In this review we will explore how the pleiotropic immune effects of retinoids intersects with HIV pathogenesis, and how retinoids can enhance intrinsic antiviral mechanisms to inform potential therapeutic applications of retinoids in HIV cure.

Natural functions of retinoids

Retinoids are defined as Vitamin A and its natural or synthetic analogues that have 4 isoprenoid units linked sequentially head to tail (11, 12). Humans ingest retinoids as retinyl esters or carotenoids (most importantly β-carotene) *via* intestinal epithelial cells. Vitamin A is then esterified and transported to the liver or target tissues packaged in chylomicrons. At these sites hydrolysis releases retinol which is taken up by the cell. There retinol is hydrolyzed to form retinaldehyde by alcohol dehydrogenase. Retinoic acid (RA), the active metabolite, is then formed by retinaldehyde dehydrogenase which is only present in certain cell types, allowing for restriction of RA activity. RA can then be transported to the nucleus and promote expression of RA-target genes *via* nuclear Retinoic Acid Receptors (RARs) and retinoid X receptors acting on specific RA response elements (RARE) (13). Vitamin A deficiency has detrimental effects on: stem cell differentiation, embryogenesis, epithelial cell development and barrier function, and innate and acquired immune cell function (12), while excessive Vitamin A can have toxic effects (14, 15). The impact of RA on immune function is complex, often paradoxical, and determined by local concentration, cell types involved, and expression of receptors, cofactors, and other cytokines. RA can therefore have both anti- and pro-inflammatory functions facilitating nuanced control of immunity (13).

Retinoids as therapeutics

Retinoids have long been used in treatment of malignancies (15–18) and dermatological diseases (19–26). All trans retinoic acid (ATRA) ($t_{1/2}$ 0.5-2h) is used in high-dose pulsed regimens to treat acute promyelocytic leukemia (16). Acitretin ($t_{1/2}$ 49h) is effectively used to treat chronic conditions such as psoriasis (20, 23, 27). Moreover, acitretin has been used safely to treat psoriasis in HIV-infected individuals (19, 22, 26). Retinoids have a long record of use, well-documented safety data, and pharmacodynamic flexibility, making them attractive targets for novel therapeutic applications.

Pleiotropic interplay between retinoids and HIV-1 infection

Modulation of CD4+ T cell activity

HIV infection of CD4+ T cell occurs when virions bind to CD4 on the cell surface followed by an interaction with chemokine receptors CCR5 or CXCR4 (28) which act as required co-receptors for viral entry. In CCR6+ T cells, which contribute to mucosal immunity in the gut, exposure to ATRA increases expression of CCR5 and CXCR4 and may lead to increased local permissiveness of HIV infection (29). Another co-receptors that acts as a direct or indirect target for HIV cellular infection is integrin α4β7, whose expression is also upregulated in response to RA (30).

RA has been shown to affect the balance between Th1 and Th2 CD4+ T cells, in a manner dependent on their stage of development. In naïve T cells, RA favors Th2 over Th1 polarization (31), yet, in already polarized Th1 effector cells RA prevents conversion into other T helper subtypes. The effect of RA can be augmented by local cytokines including TGF-β, IL-12, and IL-27 produced by antigen presenting cells, converting CD4+ T helper cells into unique MHC class-II restricted cytotoxic T lymphocytes (CTL) thought to be important for maintaining intestinal mucosal barrier function (32).

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RA induces accumulation of high-affinity CD8+ T cells at the mucosal barrier

In a similar paradigm to RA-induced CD4+ MHC class-II restricted CTLs, RA fosters selective accumulation of the most effective CD8+ T cells at the mucosal barrier. In mice, exposure to ATRA during vaccination with a replication-defective recombinant adenovirus vector expressing LCMV glycoprotein (LCMVgp) led to increased effector and memory CD8+ T cells and conferred resistance against further challenge with recombinant vaccinia virus expressing LCMVgp (33). This suggests RA can act as an adjuvant enhancing CTL responses to previously encountered viral epitopes. Exogenous RA may promote a more robust CD8+ T cell response against HIV at mucosal barriers in particular – a critical site of viral reactivation and replication.

RA promotes migration and sequestration of effector CD4+ T cells to the mucosal barrier

Central memory (CM) CD4+ T cells express CCR7 as a homodimer and a heterodimer with CXCR4. CCR7 facilitates migration of T cells to lymph nodes. Viral gp120 expression in HIV-infected cells enhances this migration, promoting escape from the site of initial infection and systemic propagation of HIV (34, 35). In addition, sequestering T cells inside lymph nodes prevents them from acting as effector cells at the mucosal barrier, impairing local mucosal immune response (36). In an *in vitro* model, dendritic cells expressing CXCR4 and CCR7 exposed to retinoids were prevented from migrating towards CCL19, the chemokine responsible for lymph node homing (37). The mechanism appears to be dual inhibition of CXCR4 and CCR7, suggesting retinoids may prevent migration of HIV-infected T cells to central immune tissue. Similarly, mucosal T cell gut-homing receptor CCR9 is induced in the presence of RA (38). Notably in central lymphoid tissue such as the spleen, the concentration of RA is low, preventing re-trafficking of T cells back to mucosal surfaces (39). Together, these data suggest that supplementation with exogenous retinoids could both induce migration of T cells to mucosal tissue *via* CCR9, and sequester them at the mucosal barrier by suppressing CXCR4 and CCR7-induced migration, limiting HIV dissemination and improving barrier competency.

In chronic HIV infection, HIV disrupts normal mucosal barrier function by depleting Th17 CCR6+ T cells, inducing anergy against HIV infected cells, and interfering with anti-inflammatory mechanisms leading a pro-inflammatory state favorable to HIV replication (29). Clearly, local physiologic production of RA is insufficient to control HIV infection. However, treatment with exogenous retinoids achieving supraphysiologic concentrations could help restore mucosal immunity *via* accumulation of high-affinity CD8+ T cells at the mucosal barrier, induction of unique MHC class-II restricted cytotoxic T lymphocytes (CTL), and trafficking of T cells to mucosal tissue that altogether may enhance clearance of reactivated HIV.

RIG-I intracellular immunity is abrogated by HIV

Innate immunity is the first line of defense against infection. It is activated after detection of conserved pathogen-associated molecular patterns by pattern-recognition receptors (PRRs). Multiple PRRs are expressed to effectively survey the interstitial environment and the various intracellular compartments. One family are the retinoic acid-inducible gene-I (RIG-I)-like receptors, named for the prototypical member RIG-I, whose expression is induced by retinoic acid (40). RIG-I serves as a cytoplasmic sensor, detecting a variety of RNA viruses, and initiates a signaling cascade resulting in Type 1 interferon production and antiviral gene expression.

Activated RIG-I functions through two signaling pathways: *via* TRAF6 resulting in NF-κB activation through the canonical pathway and *via* TRAF3 leading to activation of IRF3/7. These effectors, along with ATF2, c-jun, and p300/CBP coordinate interferon and pro-inflammatory gene expression and increase expression of RIG-1, allowing for positive feedback (41). Separate from its function as a transcriptional activator, IRF3 can trigger apoptosis *via* the RLR-induced IRF3-mediated pathway of apoptosis (RIPA) (42).

HIV disrupts RIG-I signaling by decreasing stability of IRF3 through a Vpr-induced ubiquination leading to proteosome degradation (43), yet NF-κB signaling remains intact and capable of driving HIV transcription. RIG-I signaling is also inhibited by HIV *via* sequestration dependent on the HIV protease, specifically by shuttling RIG-I into the lysosomal compartment for degradation (44). However, HIV viral production is significantly decreased if IRF3 production is restored, suggesting that RIG-I mediated intracellular immunity is capable of controlling HIV (45). Overcoming HIV-mediated attenuation of IRF3 signaling may be critical to controlling HIV infection.

Acitretin induces reactivation of HIV

Activated NF-κB drives HIV-1 transcription through multiple mechanisms. NF-κB can directly bind to regions of the HIV 5'LTR and induce HIV transcription through a cooperative interaction with transcription factor Sp1 (46, 47). In latency, p50/p50 homodimers are bound to the HIV-1 5' LTR and recruit HDAC-1 resulting in histone deacetylation and

chromatin condensation which silences HIV gene expression (48). Activated NF-κB p50/RelA heterodimers displace the p50/p50 homodimer and instead recruit histone acetyl-transferases including p300/CBP allowing for transcription of HIV *via* histone acetylation (49). This leads to increased expression of HIV-encoded Tat which aids in elongation of the HIV transcript by binding to the TAR sequence of HIV transcripts and recruiting the P-TEFb complex (50); this complex phosphorylates the C-terminal domain of RNA Pol II which increases processivity (51) and phosphorylates DSIF and NELF which removes the block to elongation (52). Tat can also be acetylated at two sites including lysine 50 by CBP/p300, which allows for a switch from early to late phase in HIV transcription elongation (53). As such, NF-κB stimulators are considered a potent class of LRAs. Their clinical utility is limited by a lack of specificity to HIV-infected cells and the potential for severe adverse reactions including life-threatening systemic inflammatory responses from global NF-κB activation (3).

In Li et al., latently HIV infected cell line ACH-2 treated with acitretin or vorinostat, a histone deacetylase inhibitor (HDACi), for 72 hours caused significant HIV reactivation (54). The acitretin-mediated reactivation was blocked by addition of curcumin, an inhibitor of p300. Increased HIV RNA expression was also observed after TZM-bl cells actively infected with GM-HIV (a *gag*-mutated NL4-3 HIV-1 clone) were treated with acitretin. Western blot analysis revealed increased p300 expression. These data indicate that reactivation of HIV occurs through stimulation of the RIG-I pathway. However, increased HIV expression in acitretin-treated cells was partially maintained in a RIG-I shRNA knockdown, so acitretin may drive expression of HIV through a pathway independent of RIG-I. Garcia-Vidal et al. did not observe significant HIV reactivation in acitretin-treated J-Lat cells [54], but a lack of reactivation after treatment with the potent LRA vorinostat [55, 56] in this study suggests that those results may be due to aspects of their experimental system.

Planas et al. examined the effect of ATRA on Th17-polarized CD4+ T cells, which are important in maintaining the gut barrier (55), and constitute a key reservoir of latent HIV infection (56). The CCR6+ subset of these cells demonstrated increased permissiveness to HIV infection. Stimulation of CCR6 + CD4+ T cells taken from HIV-infected individuals on ART with ATRA led to HIV reactivation (57). The effect was significantly decreased when the cells were treated with INK128, an inhibitor of mTOR1/2, indicating the effect is at least partly mTOR dependent.

Retinoids enhance RIG-I mediated control of HIV infection

Li et al. (54) demonstrated that treatment with acitretin decreased HIV DNA levels in infected cells, reflecting clearance of the reservoir. Specifically, treatment of GM-HIV-infected TZM-bl cells with acitretin resulted in undetectable GM-HIV DNA levels. In an *ex vivo* model of CD4+ T cells derived from 12 HIV-infected ART-suppressed subjects, acitretin resulted in a significant decrease in HIV DNA levels, which was enhanced by addition of vorinostat suggesting synergy between the two pathways. Analysis of acitretin-treated HIV-infected cells revealed a relative increase of apoptotic cells and caspase-3 activity, indicating that depletion of HIV DNA was at least partly due to acitretin-induced apoptosis of infected cells. Further testing on the TZN-bl cells revealed that acitretin treatment led to increased expression of RIG-I, phosphorylated and non-phosphorylated IRF3, and increased Bax suggesting that depletion of detectable HIV DNA occurred through stimulation of the RIG-I pathway and RIPA-mediated apoptosis. In HIV-uninfected cells, acitretin induced significantly less upregulation of these genes, and cell apoptosis rates were unchanged, suggesting the presence of viral RNA is critical to activation of the enhanced RIG-I pathway and that off-target effects could be minimal in uninfected cells.

Garcia-Vidal et al. (58) examined the effect of acitretin on multiple T cell lines and primary T cells infected with the HIV clone NL4-3 HIG, demonstrating that acitretin could induce increased RIG-I and phosphorylated IRF3, but that this effect was minimal. In J-Hig cells (J-Lat cells latently infected with NL4-3 HIG) the percentage of apoptotic cells was determined after treatment with increasing acitretin concentrations. In this model, the percentage of apoptosis in the cells where the HIV persisted in latency remained unchanged, and, in cells where HIV reactivated, only a small proportion underwent apoptosis. This called into question if acitretin was an effective enhancer of RIG-I mediated HIV clearance.

There are some important differences between the experiments in these studies that may explain the discrepancy. First, the HIV clone used in Garcia-Vidal contained a *nef*-deletion. HIV-1 Nef interacts with several intracellular proteins involved in kinase signaling pathways and endosomal trafficking. Through interaction with the Itk kinase it activates phospholipase C, eventually resulting in activation of NFAT and NF-κB, both of which drive HIV-1 transcription at the 5' LTR (59). Loss of Nef could lead to reduction in HIV-1 proviral transcription and failure to activate the primed RIG-I system, avoiding further RIG-I mediated NF-κB activation and RIPA-mediated apoptosis. Furthermore, the apoptosis experiments in Garcia-Vidal examined HIV reactivation and apoptosis together. If acitretin's latency reversal activity is more modest, as their study suggests, then it is difficult to infer the contribution of acitretin to RIG-I mediated induction of apoptosis. In Li et al., the most dramatic effect of acitretin occurred in *ex vivo* T cells derived from (*nef* intact) HIV-infected individuals fully suppressed on ART (54). Subsequent work by Planas et al. showed that RIG-I expression was induced in CCR6 + and CRR6 - T cells in the presence of ATRA, but impact on clearance of HIV-infected cells was not explored (57). Further study is required to illuminate how acitretin's enhancement of RIG-I functions *in vivo* and in the presence of established HIV infection.

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Potential HIV cure shocktails

To date no approach, let alone a single agent, has been shown to effectively purge the latent HIV reservoir in established infection. Since HIV latency is a multifactorial process, it may be that only multi-drug regimens, which we have termed shocktails, will be able to sufficiently reverse latency (60). The challenge is identifying agents that act synergistically to promote HIV latency reversal and immune clearance with minimal toxicity. Several reviews have been written about the numerous compounds that are being studied as potential cure agents (3), all of which are limited by their lack of specificity; for example, the NF-κB stimulators like prostratin cause global transcriptional activation leading to significant toxicity. Retinoids, in contrast, enhance RIG-I mediated intracellular immunity partly through NF-κB activation which is triggered only in the presence of viral products, for exquisite specificity. This specificity for infected cells makes retinoids attractive agents as the backbone of cure shocktails. By understanding the molecular biology of retinoids, we can speculate about which other candidate compounds could be added to a retinoid-based shocktail as summarized in Figure 1.

HDACi, including FDA-approved agents vorinostat, romidepsin, panobinostat, and valproic acid have all been shown to induce HIV reactivation *in vivo* (61–64), but have dose-dependent side effects that limit their application. Enhanced clearance of latently-infected cells treated with both vorinostat and acitretin has been observed *in vitro* and could be explained by stimulation of the RIG-I pathway by HDACi-induced HIV transcription (54). Another HDACi, Trichostatin A (65) was shown to induce expression of IRF-3 when combined with valproic acid (66), which could counter HIV Vpr-mediated IRF-3 depletion and restore RIG-I activity. It remains unclear if increasing IRF-3 expression is a property shared by other HDACi.

Vpr inhibitors are attractive potential agents to combine with retinoids. In addition to IRF-3 suppression, Vpr impacts host cell functions including energy metabolism, oxidative status, and proteasome function that are involved in HIV pathogenesis (67). Vpr inhibition is an attractive target for future therapies, and several potential molecules have been isolated that inhibit Vpr *in vitro* (68).

Inhibitors of apoptosis (IAPs) prevent apoptosis directly, where XIAP binds and inhibits caspases, or indirectly, where cIAP1/2 prevents the assembly of pro-apoptotic signaling complexes. cIAPs

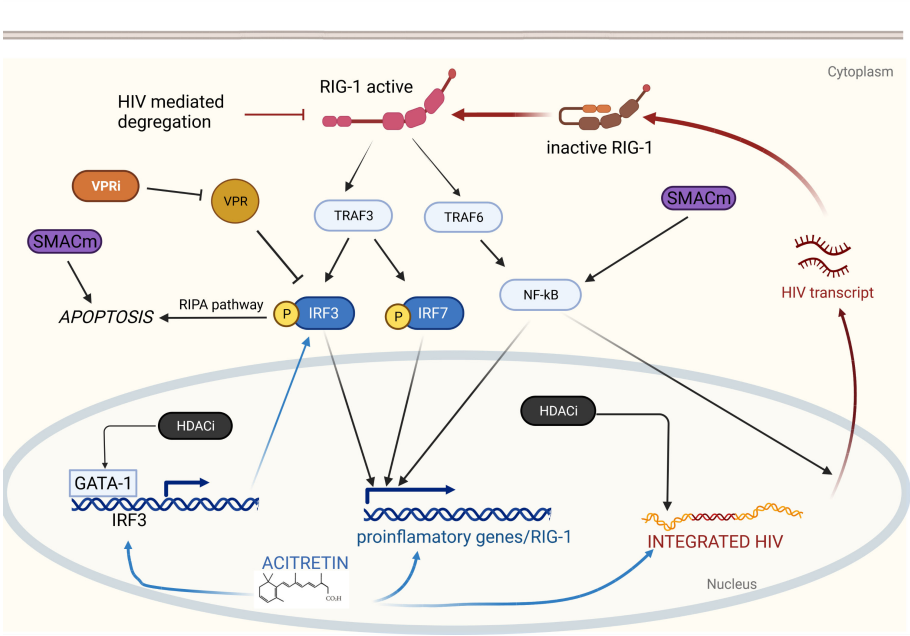

FIGURE 1
Retinoids induce HIV reactivation and enhance immunity via RIG-I. RIG-I detects intracellular HIV RNA resulting in TRAF3 and TRAF6 activation. TRAF6 elicits a signaling cascade releasing NF-κB which translocates to the nucleus and drives proinflammatory gene expression and HIV transcription. TRAF3 induces phosphorylation of IRF3 and IRF7 which also drive proinflammatory gene expression. Phosphorylated IRF3 can also induce apoptosis via the RIPA pathway. Acitretin enhances expression of IRF3, RIG-I, and proinflammatory genes as well as HIV transcription leading to reactivation of latent HIV infection and immune mediated clearance. Combination with additional therapeutics may enhance acitretin activity allowing for HIV eradication. HDACi increase HIV expression leading to further stimulation of the RIG-I pathway and increase expression IRF3 potentially overcoming HIV-mediated inhibition. VPR inhibitors may directly prevent VPR-mediated suppression of IRF3. SMACm increase NF-κB expression stimulating HIV transcription which can then activate RIG-I. SMACm are also pro-apoptotic and may function synergistically with the RIPA pathway.

also act as negative regulators of canonical and non-canonical IKKα-dependent NF-κB pathways. SMAC mimetics (SMACm) (69) suppress cIAPs and XIAP leading to NF-κB activation and disinhibition of cell death. SMACm have been shown *in vitro* and *in vivo* to induce robust HIV reactivation and exhibit synergy with the HDACi panobinostat (70, 71). Furthermore, compared to prior NF-κB stimulators, SMACm appear to be well tolerated in animal models; the SMACm AZD5582 was shown to reverse latency in SIV infected rhesus macques without inducing global CD4+ T cell activation or significant toxicity (71). By activating the non-canonical IKKα-dependent NF-κB pathway, SMACm could potentially work synergistically with retinoid-induced RIG-I activation *via* the NF-κB canonical pathway. Since, the synergistic activation would likely be restricted to HIV infected cells, it is expected that the combination would be tolerated. However, there remains theoretical potential for toxicity.

Retinoids: future directions in HIV cure research

Eradicating the latently infected reservoir remains the major hurdle in curing HIV. Retinoids have potent latency reversal activity and are capable of purging HIV-infected cells through enhanced RIG-I-mediated immunity and RIPA-induced apoptosis. Retinoids also influence many aspects of the immune system; including enriching high-affinity CD8+ CTLs with potential enhanced anti-HIV properties, re-trafficking of CD4+ and CD8+ T cells toward depleted mucosal barriers, and halting central spread of HIV. While there is concern that retinoids may increase local permissiveness of HIV infection, enhancement of immune clearance or combination with ongoing ART may render this irrelevant. RA should be further explored as a potential therapy in the pursuit of a cure for HIV. The unique mechanism of retinoids in countering HIV infection and its apparent restriction to infected cells, suggest retinoids could form the backbone of potential shocktails. Given its robust safety data, further research assessing retinoids alone and in combination with other "Shock and Kill" candidates in human trials is the next step in determining the place of retinoids in the arsenal for HIV cure.

Author contributions

AP - first author, conceptualize the review, manuscript preparation, literature search. MM - manuscript preparation. BV - figure preparation, manuscript revisions. JA - corresponding author, manuscript revisions. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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