MINI REVIEW

Recent advances targeting innate immunity-mediated therapies against HIV-1 infection

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ABSTRACT

Early defence mechanisms of innate immunity respond rapidly to infection against HIV-1 in the genital mucosa. Additionally, innate immunity optimises effective adaptive immune responses against persistent HIV infection. Recent research has highlighted the intrinsic roles of apolipoprotein B mRNA-editing, enzyme-catalytic, polypeptide-like 3G, tripartite motif-containing protein 5, tetherin, sterile α-motif and histidine/aspartic acid domain-containing protein 1 in restricting HIV-1 replication. Likewise, certain endogenously secreted antimicrobial peptides, namely α/β/θ-defensins, lactoferrins, secretory leukocyte protease inhibitor, trappin-2/elafin and macrophage inflammatory protein-3α are reportedly protective. Whilst certain factors directly inhibit HIV, others can be permissive. Interferon-λ3 exerts an anti-HIV function by activating Janus kinase-signal transducer and activator of transcription-mediated innate responses. Morphine has been found to impair intracellular innate immunity, contributing to HIV establishment in macrophages. Interestingly, protegrin-1 could be used therapeutically to inhibit early HIV-1 establishment. Moreover, chloroquine inhibits plasmacytoid dendritic cell activation and improves effective T-cell responses. This minireview summarizes the recently identified targets for innate immunity-mediated therapies and outlines the challenges that lie ahead in improving treatment of HIV infection.

Key words apolipoprotein B mRNA-editing, enzyme-catalytic, polypeptide-like 3G; HIV-1; SAM-histidine/aspartic acid (HD) domain-containing protein 1; therapies.

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List of Abbreviations: APC, antigen presenting cell; APOBEC3G, apolipoprotein B mRNA-editing, enzyme-catalytic, polypeptide-like 3G; ART, antiretroviral therapy; BST, bone marrow stromal antigen 2; CA, capsid; CCR5, C-C-chemokine receptor 5; cDNA, copy DNA; CTL, cytotoxic T lymphocytes; CXCR4, C-X-C-chemokine receptor 4; CypA, cyclophilin A; DC, dendritic cell; dsRNA, double-stranded ribonucleic acid; GalCer, galactosylceramide; GM-CSF, granulocyte-macrophage colony stimulating factor; gp120, glycoprotein 120; hA3G, human APOBEC3G; HsP70, heat shock protein 70; IDO, indoleamine 2, 3, dioxygenase enzyme; IFN, interferon; IRF, IFN-regulatory factor; IL, interleukin; ISG56, IFN-stimulated gene 56; JAK-STAT, Janus kinase-signal transducer and activator of transcription; kDa, kilodaltons; LC, Langerhans cell; LIF, leukemia inhibitory factor; LMM, low molecular mass; 1-MT, 1-methyl tryptophan; MAMP, microbe-associated molecular pattern; MDA5, melanoma differentiation-associated protein 5; MDC, macrophage-derived chemokine; MIP-3α, macrophage inflammatory protein-3α; Mxα, myxovirus A protein; NALP, NACHT, LRR and PYD domains-containing protein 3; NOD, nucleotide-binding oligomerization domain; NK, natural killer; NLRP, NOD-leucine rich repeat and pyrin domain-containing protein 3; PBMC, peripheral blood mononuclear cells; PC, Paneth cell; PDL-1, programmed death ligand-1; pDC, plasmacytoid dendritic cell; PEI, polyethylene glycol; Pf74, Pf-3450074; protegrin-1; PIAS-1, protein inhibitor of activated STAT-1; Poly I:C, polyinosinic acid:polycytidylic acid; RA LMM, raft-associated LMM; RANTES, regulated on activation of normal T-cell expressed and secreted; rhIFN-β, recombinant human IFN-β; RIG-1, retinoic acid-inducible gene-1; SAM, sterile alpha motif; SAMHD1, SAM-histidine/aspartic acid (HD) domain-containing protein 1; SDF-1, stroma-derived protein-1; SIVmac, simian immunodeficiency virus rhesus macaque; SLPI, secretory leukocyte protease inhibitor; SNP, single nucleotide polymorphism; TLR, Toll-like receptor 1; TNF-α, tumor necrosis factor-alpha; TREX1, three prime exonuclease 1; TRIM5α, tripartite motif-containing protein 5; Vif, virion infectivity factor; Vpx, viral protein U; WAP, whey acidic proteins.
Human immunodeficiency virus 1 has emerged as a major threat to humankind and understanding host immune responses against this virus has become a major challenge for scientists (1, 2). Over the years, the virus has evolved the ability to evade host immune responses efficiently, and treatment strategies for controlling virus replication in infected individuals have led to emergence of drug-resistant strains. Although morbidity and mortality rates have decreased dramatically, ART nonetheless has its own array of complications (1). Further, both vaccine trials and microbiocide development have taken a backseat and failed to make a mark in disease prevention. Understanding the importance of innate immunity and disease susceptibility is currently the area of greatest priority in HIV research. There is an urgent need to extend potential alternate therapeutic options, especially those targeted at boosting the innate immune system (1–3).

The hallmark of innate immunity is its rapid ability to recognize a series of MAMPs that initiate first-line effector responses (3, 4) via a range of immune sensors, namely, TLRs, RIG-I-like receptors, NOD-like receptors and cytosolic DNA receptors, all of which mediate key innate pathways. Recent advances in our understanding of innate defense attributes for preventing infection using novel therapeutic targets remain to be reviewed. Hence, this review focuses on recent advances in understanding of the roles of therapeutic approaches intended to target host innate immune responses, with a view to designing strategies for preventing HIV acquisition.

**CELLULAR AND SOLUBLE INNATE RESPONSES AT SITES OF MUCOSAL HIV ENTRY**

Soluble and cellular/intracellular innate responses in the mucosal layers of the genitourinary tract offers efficient first line defense against HIV-1 infection. Cellular innate immunity includes DCs and LCs that come into contact with HIV-1 in the mucosa, where trans-infection of CD4+ T cells can occur, leading to dissemination of the virus throughout the host system. On the other hand, intracellular innate immunity also includes intrinsic immunity, which is mediated by host factors with pivotal roles in restricting HIV-1 replication such as APOBEC3G, TRIM5α, tetherin (BST-2/CD317/HM1.24), TREX1, SAM and SAMHD1. Likewise, certain endogenously secreted antimicrobial peptides, namely α/β defensins, θ-defensins (cyclic octadecapeptide retrocyclins), lactoferrins, SLPI, trappin-2/elafin and MIP-3α have been found to protect the host against HIV acquisition (5–10). Recent research has unraveled the contribution of inflammasome genes to HIV-1 acquisition. SNPs within NLRP3 (rs10754558) and IL-1β genes (rs1143634) are significantly associated with HIV-1 infection, suggesting involvement of NALP3-inflammasome in HIV-1 pathogenesis and that innate immunity could regulate factors determining susceptibility to HIV-1 infection (11). Although certain factors like human β-defensins 2 directly inhibit HIV (6), others, namely SDF-1α, RANTES, MIP-1α, and MIP-1β reportedly prevent viral entry (10). The role of certain synthetic components and their potentials for boosting innate immune responses to contain HIV infection has also been discussed.

**SMALL MOLECULES AND CYTOKINES**

**Defensins**

Defensins are small cationic antimicrobial peptides that confer innate resistance against a broad spectrum of pathogens at the site of entry. According to their disulfide bonding patterns, defensins are classified into three subfamilies namely α, β, and θ defensins. α-defensins are expressed by neutrophils, lymphocytes, intestinal PCs, and epithelial cells lining the cutaneous, urogenital and respiratory (β-defensins) tracts. While certain defensins (defensins 5 and 6) aid HIV entry by inhibiting HIV-suppressive polyanions at mucosal sites, certain others confer protection. Defensins promote secretion of proinflammatory cytokines and can attract T cells and APCs (DC and T cell chemotaxis) to enhance HIV-1 infection (12, 13). Nonetheless, defensins of PCs reportedly protect the gut mucosa of primates from opportunistic pathogens (14). Defensins also reportedly block HIV attachment via impairment of gp120 and coreceptor down-regulation, fusion, and enhancement of intracellular HIV restriction (15–16). Further, altered defensin concentrations have been correlated with neutrophil dysfunctions in HIV disease.

Although α and β-defensins are functionally effective, θ-defensins (cyclic octadecapeptide retrocyclins) are often inert. Humans are known to have numerous θ-defensin genes. The human genome reportedly has a premature termination codon that blocks translation of θ-defensin gene; hence this gene is not expressed as peptides and is not functionally active (i.e. it is a pseudogene) (reviewed in 17). So, is it feasible to reincarnate the retrocyclin anti-HIV machinery from its remnants? Hopefully, the time has come to clarify this! Retrocyclin represents an ancestral “dead” human cationic θ-defensin (18–20) that reportedly interferes with early viral entry. Hence, it is proposed that retrocyclin-like agents could serve as topical anti-HIV agents (21). Retrocyclin confers protection from HIV by binding to carbohydrate-containing moieties on cell
surfaces. Research strategies employing forensic approaches to re-assembling retrocyclin from its remains have shown that it has remarkable potential to protect against HIV infection (21). Although it is uncertain whether its evolutionary loss actually contributed to the vulnerability of humans to HIV infection, synthetic retrocyclin is definitely a likely topical microbicide candidate against HIV infection. Measures to fine-tune the effects of defensins at sites of potential mucosal HIV entry could be a promising therapeutic approach for future research.

**β-chemokines**

Hosts have a plethora of chemokines that are effective at conferring protection from establishment of HIV-1 in them. Binding of natural ligands (of CCR5 chemokine receptors), namely, MIP-1α, MIP-1β, and RANTES, confers protection against R5 viruses during the early stages of HIV infection, whereas in the chronic stages of HIV infection SDF-1/2 binds to CXCR4 on T cells and protects from X4 viruses (22–25). Binding of RANTES to CCR5 chemokine receptor blocks HIV fusion directly or via CCR5-mediated down-regulation to delay HIV disease progression. MIP-1α concentrations are reportedly increased by GalCer molecules in the islets of the pancreas (26), whereas sulfated polyglycans (FucS) dramatically increase circulating SDF-1 concentrations (27). Ironically, in vaccination studies β-chemokine-mediated viral control demonstrated in vitro has failed to occur in vivo. Intriguingly, high MIP-1α/β concentrations have been associated with increased viral persistence and rapid disease progression (28–30) and SDF-1 does not block HIV-1 spread in vivo (33, 34). Adding to this list of contrasting conclusions, one study reported that polymorphisms in SDF-1 gene can delay the onset of AIDS by increasing amounts of SDF-1 available for binding to CXCR4 (32), whereas others have reported an association of such polymorphisms with rapid disease progression (31, 33, 34). Certain other chemokines such as MIP-3α, a known chemo-attractant of immature DCs and lymphocytes, are HIV permissive. Although, MIP-3α has anti-microbial activities, in the presence of seminal vaginal epithelial cells secrete enormous amounts of MIP-3α, culminating in chemotaxis of the LCs that uptake HIV (35). Hence, β-chemokines can trigger target CD4+ T cell accumulation in lymph nodes resulting in enhanced retroviral replication. I-309 is a recently described CCR8 antagonist β-chemokine that blocks the entry of X4 viruses (36). Therefore, approaches to triggering conditioned endogenous activation of β-chemokines are considered potential anti-HIV therapeutic approaches that needs further investigation.

**Other cytokines**

Recent research has shown that certain other cytokines exhibit anti-HIV activities. IFN-λ, newly reported IFNs, comprise three forms IFN-λ1, IFN-λ2, and IFN-λ3 (37, 38). Recent research has shown that IFN-λ3 can efficiently suppress replication of viruses in macrophages (39). It also suggests that IFN-λ3 significantly inhibits viral multiplication by recruiting certain antiviral restriction factors, namely, ISG56, MxA, OAS-1, APOBEC3G/F and tetherin, and IFN regulatory factors, IRF-1, 3, 5, 7 and 9 (37, 38). The research also shows that IFN-λ3 is more potent in suppressing HIV than IFN-λ1 and IFN-λ2, and that the JAK-STAT signaling pathway is responsible for triggering the antiviral effects of IFN-λ3 (39). This study has highlighted the precise anti-HIV roles of IFN-λ3, offering an opportunity for controlling viral establishment. Hence, studies must aim at exploring the potential for developing IFN-λ3-based therapies against HIV infection.

On the other hand, interesting recent research has shown that morphine significantly inhibits expression of IFN-α, IFN-β, IFN-λ, and APOBEC3C/3F/3G and 3H (40). In addition, this study reported that morphine suppresses expression of several other key innate immune elements in the IFN signaling pathway, namely RIG-I and IRF-7. In addition, morphine triggers up regulation of suppressor of cytokine signaling proteins 1, 2 and 3 and protein inhibitors of activated STAT1, 3, X and Y (PIAS-1, 3, X, Y), the key negative regulators of the IFN signaling pathway (40). These findings show that morphine impairs intracellular innate antiviral mechanism(s) in macrophages, contributing to susceptibility to HIV infection.

CD8+ T cells are the key components of adaptive immune responses. However, HIV-specific CD8+ T cells also reportedly contribute to certain non-cytolytic innate immune functions (41). Activated CD8+ T cells have been shown to confer entry inhibition via secretion of MIP-1α, MIP-1β and RANTES. Further, they also produce IL-16, which naturally binds CD4 receptors and denies entry of HIV-1 (41, 42). CD8+ T cells also secrete MDC (43, 44), LIF (45), thioredoxin and IL-13 (46, 47), which can serve as non-entry inhibitors. Recent studies have shown that ART improves C-C-chemokine concentrations, leading to better clinical outcome (48). Hence, the interaction between chemokines and protective factors produced by non-cytolytic CD8+ T cells is likely to find applications in conjunction with ART or vaccines.

**Whey acidic proteins**

Whey acidic proteins are soluble mediators that can efficiently regulate both HIV replication and innate and
adaptive immune responses. SLPIs, WAPs found in mucosal secretions (49), reportedly reduce the risk of perinatal HIV transmission (50). SLPI exerts anti-HIV activity by forming a complex with human scramblase to block viral fusion with host cell membranes (31, 51, 52). On the other hand, it can also act by impairing annexin II, which promotes viral fusion following gp160 linkage with CD4 and CCR5/CXCR4 (53, 54) and, hence, can be pleiotropic. Therefore, it remains to be established whether recombinant forms of SLPI could serve as therapeutic agents by bringing about blockade of the innate pathways that support HIV replication. Trappin-2/elafin is another WAP produced by epithelial cells that directly interacts with HIV, reducing its infectivity (1). Trappin-2/elafin can also bind to HIV-binding sites on T cells, impede HIV entry (55), and serve as a potent endogenous anti-HIV microbicide (55, 56). Studies have shown that women produce high concentrations of genital trappin-2/elafin during the secretory phase of the menstrual cycle, which inhibits HIV infection (56). Hence, the use of trappin-2/elafin as a therapeutic modality against HIV transmission is an area that is worth investigating.

**PLASMACYTOID DENDRITIC CELLS**

**Type I interferons**

Type I interferon (IFN-α/β) responses represent the canonical innate immune response against persistent viral agents. Recent lines of evidence show that elite controllers have pDCs that efficiently control HIV replication (57). Research suggests that type I IFN responses may play a pivotal role in both viral control and progressive HIV infection. In response to stimulation of endosomal TLRs 7 and 9 by viral nucleic acids, pDCs produce IFN-α/β. In both primary and chronic HIV disease, type I IFN decreases concomitantly with a decrease in the numbers of circulating pDCs (58) (possibly due to expression of CD4, CXCR4, and CCR5 by pDCs). Type I IFNs are known to contribute to HIV control by increasing the IFN-γ secreting ability of CD4+ T cells (59, 60). Recombinant human IFN-β and IFN-α are effective in suppressing HIV (61). One study suggests a therapeutic role for PEG-IFN in primary HIV infection when the numbers of IFN-α producing-pDC start to decline (62, 63). However, a variety of other pDC surface molecules are known to regulate the amplitude of IFN-α/β responses. Likewise, HIV-activated pDCs may contribute to certain detrimental effects on HIV disease progression. Some of the deleterious effects of persistently activated pDCs and persistent IFN production are thought to be mediated by IDO produced by pDCs. HIV-activated pDCs are known to express IDO, which triggers immunosuppression (64, 65). Extended presence of IFN-α/β also upregulates CD8+ T-cell activation markers, leading to progressive depletion of bystander CD4+ T cells (66–69). Use of chloroquine blocks TLR signaling, blocking IFN-α release, and curtails activation of pDCs and subsequent release of IDO and PDL-1, leading to effective adaptive immunity (reviewed in 1). Hence, therapeutic strategies aimed at fine-tuning pDC function to create a homeostatic microenvironment to efficiently control infection, especially robust secretion of type I IFNs at the early stages are important, because persistent activation can lead to exaggerated immune activation, culminating in immune exhaustion and senescence (70, 71).

**Kynurenine pathway**

Control of tryptophan metabolism by IDO in pDCs is a highly versatile modulator of innate immunity (reviewed in 1). HIV-1 reportedly stimulates pDCs to secrete IDO, neutralizing the effects of IFN-γ responses, and prevents hyperinflammatory Th17 responses (72). IDO is believed to prevent uncontrolled immune responses in chronic infections. On the other hand, increased IDO secretion by DCs during acute and chronic viral infections has been reported (72–78). IDO-expressing pDCs are tolerogenic, thus they prevent autoimmunity (73) and maternal-fetal recognition during pregnancy (76). Hence, a balance in IDO concentrations to facilitate viral clearance may be a pre-requisite when targeting the kynurenine pathway (73–77). Research has shown that, in HIV-infected patients, IDO blockade of pDCs improves 1-MT antiviral potentials and T-cell responses (78). Animals treated with 1-MT have increased CD3+, CD8+, CD8+/I-γ+ T cells, and HIV-1gag/pol-specific CTLs in their peripheral blood. In addition, blockade of gp120/CD4 interactions using anti-CD4 antibodies inhibits HIV-mediated IDO induction. Recruitment of IDO by HIV in pDCs leads to T cell dysfunction via a non–IFN-dependent mechanism (64, 65). Hence, fine-tuning of IDO is likely to enhance HIV-specific CTL expansion leading to elimination of HIV infected cells.

**INTRINSIC ANTIVIRAL RESTRICTION FACTORS**

A plethora of host factors is effective at detecting viral infection and defending individual cells from viruses. These intrinsic natural cellular protein factors, namely APOBEC3G, TRIM5α, tetherins, SAMHD1 and TREX1 proteins, directly recognize HIV components and can rapidly block viral replication. TRIM5α reportedly possesses numerous innate cellular functions, such as cell signaling, apoptosis, and immune modulation. However, certain other cellular factors, such as CypA, can be
hijacked by HIV for its replication. Hence, there is a need to design therapeutic approaches directed at downplaying such drug targets and enhancing the efficiency of beneficial restriction factors, with minimum chances of causing virus mutation. Such an approach largely depends on identification of novel cellular factors associated with HIV replication.

Apolipoprotein B mRNA-editing, enzyme-catalytic, polypeptide-like 3G restricts HIV infectivity by hypermutating viral cDNA and inhibits reverse transcription and viral-host genome integration during the course of the HIV life cycle. However, HIV prevents APOBEC3G entry via Vif. A significant body of research has been devoted to linking type I IFNs with certain anti-HIV restriction factors. Recent studies have dissected the existence of RA LMM hA3G complex to increase understanding of the regulatory attributes of APOBEC3G regarding its antiviral and cellular functions (79–83). Enhancement of viral incorporation of APOBEC3G by increasing accumulation of the RA LMM or LMM complexes, which block its localization at lipid rafts, is believed to result in Vif-resistant post-entry HIV inhibition and could be developed into effective anti-HIV strategies. Especially during acute and primary infection, the role of APOBEC3G and other restriction factors would likely provide clues to therapeutic manipulation of restriction factors in high-risk groups. Vaccination of macaques via the rectal mucosa with SIV antigens and CCR5 peptides linked to a 70 kDa heat-shock protein (hsp70) led to progressive increase in APOBEC3G expression in PBMCs until 17 weeks. Subsequently, mucosal challenge with SIV resulted in significant up-regulation of APOBEC3G in CCR5+ memory CD4+ T cells, which provided protection from SIVmac 251 challenge in comparison to animals that were not immunized (84). Such findings suggest that mucosal immunization targets CD4+CCR5+ memory T cells that may prevent infection due to the early onset of an APOBEC3G-mediated anti-retroviral response. More studies are required to understand the role of restriction factors and their potential implications for anti-HIV therapies.

Tetherins, type II transmembrane proteins expressed on pDCs following exposure to IFNs, impede HIV release by retaining newly budded virions on the cell surface (1, 85). HIV-1 Vpu down-regulates tetherin by ubiquitin-dependent proteasomal degradation (86). Tetherin interacts with ILT7 to reduce IFN-α/β activity and inflammation by pDCs via TLR7/9 signaling (87). However, human tetherin lacks certain crucial residues that render immune cells susceptible to HIV-1 Nef (88, 89). pDCs are poorly permissive to HIV due to tetherin expression and secretion of type I IFNs. It remains to be seen whether lack of T cells devoid of tetherin would permit HIV entry and infection. Design of specific tetherin-binding agents for protecting cells from Vpu and other viral encoded countermeasures may be required. On the other hand, CypA reportedly binds HIV-1 p24 and facilitates HIV replication (90). It is believed that CypA-deficient viruses are replication-defective in T cells and macrophages, the major HIV reservoirs in infected individuals. Hence, therapeutic strategies targeting downplay of CypA have become a leading research topic in recent years. Researchers have developed a non-immunosuppressive cyclosporine analogue CypA inhibitor called Debio-025, which interferes with early HIV replication. However, it is reportedly ineffective against mutant HIV (90, 91).

The role of the cytosolic exonuclease TREX1, which suppresses type I IFN responses to help HIV evade cellular mechanisms, needs to be manipulated for potential therapeutic applications, as lack of TREX1 can boost IFN-β anti-HIV responses (92). Scientists have recently developed a small molecule HIV-1 inhibitor named PF74 that targets the CA protein to inhibit reverse transcription at early stages. Another molecule, PF74 has also been shown to trigger premature HIV-1 uncoating in target cells, mimicking the activity of TRIM5α (93). Recent research has also highlighted the role of SAM and SAMHD1 cell targets in HIV infection (94). Hence, studies aimed at therapeutically interrupting the pathways of the HIV lifecycle via cellular factors in target cells are paramount to progress in preventing HIV acquisition.

**POTENTIAL IMMUNE THERAPIES**

Numerous adjuvants, especially TLR agonists such as synthetic dsRNA (95) and poly I:C (96) can activate innate immunity. Poly I:C binds to endosomal TLR3 and MDA5 to activate IRF-3 and triggers secretion of type I IFNs (96–98). In addition, numerous hemopoietic and non-hemopoietic cells can produce type I IFNs upon adjuvant stimulation (96, 97) and initiate adaptive immune responses. The ability of cytokines, especially IL-2, IL-10, IL-12, IL-15, type I IFNs and GM-CSF; anti-TNF-α drugs like pentoxifylline and thalidomide; and immune modulators such as cyclosporin A, hydroxyurea and mycophenolic acid and thymopentin; to enhance innate immunity have been well established. IL-15 has been linked to increased NK cell activity (98–100). ART naïve subjects have low concentrations of IL-15 (100), hence the role of IL-15 can be seen as fortifying innate immune responses. Furthermore, IL-10 reduces HIV replication in vitro via its anti-TNF-α activity (100) although it can also inhibit CTL responses (101). Hence, a balance between the beneficial and detrimental effects of IL-10 may be worth investigating. IL-12 administration reportedly reduces SIV viral loads and prolongs the survival of SIVmac25’-infected rhesus macaques (102). Although the use of IL-2 and GM-CSF
yields only limited success, IL-12 has been successful in inducing non-cytolytic responses (103). Furthermore, certain soluble innate factors such as PG-1 could be used therapeutically to inhibit the early step of HIV-1 replication; the foreseeable cytotoxic effects of cathelicidin limit its use as an antiviral agent (104). Likewise, therapeutic possibilities aimed at manipulating B-1 cells, γδ T cells, neutrophils and other factors involved in maintaining good innate responses need to be thoroughly investigated.

CONCLUSIONS

HIV-1 is highly transmissible because the cellular layers lining the genital tissues are delicate and can exhibit molecules that easily permit viral entry. Complete anti-HIV-1 activity possibly requires therapeutic induction of concerted participation of the aggregate of soluble innate factors in the genital tissues to prevent establishment of HIV infection. Even if the host mucosa were enriched with numerous innate barriers that imposed a wide range of impediments to viral entry, concerted interplay of innate and acquired immune responses would still be required for HIV-1 control. Hence, strategies to stimulate the innate and adaptive immune responses that are effective at thwarting viral entry is a pre-requisite to HIV prevention. Future studies targeting the innate immune system may greatly improve our ability to effectively treat and control HIV in the near future.

DISCLOSURE

The authors declare no conflict of interest.

REFERENCES


