Emerging Concepts in the Immunopathogenesis of AIDS

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Abstract

There is an intense interplay between HIV and the immune system, and the literature is replete with studies describing various immunological phenomena associated with HIV infection. Many of these phenomena seem too broad in scope to be attributable either to HIV-infected cells or to the HIV-specific immune response. Recently, a more fundamental understanding of how HIV affects various T cells and T cell compartments has emerged. This review covers the role of immune activation in HIV immunopathogenesis, how that activation could be mediated directly by HIV replicating within and damaging the gut mucosal barrier, how HIV affects multiple T cell functions and phenotypes, and how chronic HIV replication induces immune modulatory pathways to negatively regulate certain functions in HIV-specific T cells.
**INTRODUCTION**

The interplay between HIV and the immune system that ultimately leads to loss of immune control of multiple pathogens and cancer has been termed the immunopathogenesis of AIDS. Although many basic concepts of how HIV is able to damage the immune system are unquestioned—for example, HIV infects and destroys CD4 T cells, neutralizing antibodies have little effect on virus replication, and cytotoxic T lymphocytes (CTLs) limit HIV replication without stopping it—other concepts are more controversial. Many have questioned how HIV can infect such an apparently small proportion of CD4 T cells (estimated at 1 in 100 to 1 in 1000) and yet still overwhelm the T cell renewal capacity of the immune system. Others question what is driving the chronic immune activation in HIV infection: the virus, the virus-specific immune response, or another mechanism. Within this context, controversy remains over whether the virus drives immune activation, immune activation drives virus replication, or both. Finally, although CTLs can help control virus replication, why HIV-specific CTLs fail to do a better job than they do remains an area of intense investigation.

Recent discoveries allow some unifying hypotheses to emerge. It has become clear that in the balance between viral replication and immune activation, a high and persistent level of virus replication is fundamental to the process of AIDS pathogenesis. If virus replication is blocked with antiretroviral therapy (ART), most immunological defects will revert toward normal (some more rapidly than others). However, blocking immune activation has proven much less successful in restoring the immune system’s normal state. The literature on the immunopathogenesis of AIDS, 25 years into the epidemic, is too vast to allow a comprehensive review in these pages. We touch on some newer findings that help address how HIV, by infecting certain CD4 T cells, is able to wreak such havoc on the immune system, and how the virus subverts the T cell response that is mobilized against it.

**IMMUNE ACTIVATION IN HIV INFECTION**

Chronic systemic immune activation is an almost pathognomonic feature of progressive HIV infection. Indeed, it is one of the strongest predictors of disease progression (1–4), is associated with impaired immune reconstitution in patients on ART (5), and is a critical factor that distinguishes pathogenic from nonpathogenic simian immunodeficiency virus (SIV) infection in nonhuman primates (6, 7). Manifestations of chronic immune activation include polyclonal B cell activation (8), increased T cell turnover (9), increased frequencies of T cells with an activated phenotype (10), and increased serum levels of proinflammatory cytokines and chemokines (11).

Although immune activation may have some beneficial consequences, such as T cell proliferation and, by inference, the partial restoration of tissue memory CD4 T cells (12), there is general agreement that it is overwhelmingly detrimental to the HIV-infected person. High turnover of CD4 and CD8 T cells imposes a strain on their homeostatic mechanisms (13), resulting in a decrease in the overall half-life of T cells (14), and clonal exhaustion of T cells may ultimately drain memory T cell pools (15, 16). Inflammatory damage to lymphoid tissues may underlie thymic dysfunction (17, 18) and TGF-β-mediated fibrosis of lymph nodes (19, 20), which are, in turn, associated with abnormal retention of effector-type T cells (21) and poor immune reconstitution with ART (22). Furthermore, and perhaps most importantly, immune activation results in the generation of activated T cell targets for the virus itself, further driving viral replication (23, 24). Thus, HIV is a virus that, through the induction of immune activation, generates its own substrate for replication. Critically, it is the activation, infection, and depletion of central memory CD4 T cells that are viewed, under normal circumstances, as a “self-renewing” source for tissue effector memory CD4 T cells, which may correlate most closely with progression to AIDS (12).
Thus, constant damage to the cellular sources of (and anatomical niches that maintain) the CD4 T cell compartments, caused by a quasi-self-perpetuating relationship between the virus and immune activation, further exacerbates the progressive net loss in CD4 T cell numbers and function and inevitably leads to AIDS. However, even though HIV has been shown to activate dendritic cells and natural killer (NK) cells of the innate immune system in vitro via TLR7/8 (25–27), its replication cannot alone account for the extent of systemic immune activation in HIV-infected individuals. For example, elite controllers (i.e., patients who spontaneously control viral loads to very low or undetectable levels) may have high immune activation, which also correlates with progressive CD4 T cell loss (3). Furthermore, individuals treated with ART who suppress virus but have incomplete restoration of CD4 T cells also have increased immune activation (5). Finally, in nonpathogenic SIV infection of natural hosts such as sooty mangabeys and African green monkeys, although there is high systemic immune activation in the acute phase of the infection, this is rapidly attenuated in the chronic phase, even in the presence of persistently high viral loads (28–30; for review see 7). Thus, defining the factors that underlie systemic immune activation is critical to understanding the pathogenesis of progressive HIV infection. Recent studies have provided a direct link between immune activation in chronic HIV infection and catastrophic pathogenic events that occur at the mucosal surfaces during acute infection.

THE GUT MUCOSA AND IMMUNE ACTIVATION

The mucosal surface of the gastrointestinal (GI) tract forms a unique anatomical and physiological niche, serving as a structural and immunological barrier against the microorganisms of the outside world. In fact, the majority of the body’s lymphocytes are contained in the GI tract (31, 32). It has long been known that HIV infection causes damage to this critical organ. In 1984, Kotler and colleagues observed that HIV-infected individuals had histological abnormalities of the GI mucosa, malabsorption, and lymphocyte depletion (33). More recently, a number of groups have shown that during the acute phase of HIV infection in humans, or pathogenic SIV infection in rhesus macaques, the majority of GI tract CD4 T cells are lost, likely as a result of direct viral infection (21, 34–40). Moreover, this depletion continues throughout the entire disease course and represents a considerable assault to the immune system, neither the tempo nor extent of which is reflected in peripheral blood CD4 T cell counts. In addition to the loss of CD4 T cells, gene expression profiles of GI tract biopsies reveal that genes associated with cell cycle regulation, lipid metabolism, and epithelial cell barrier and digestive functions are downregulated in HIV-infected individuals (41). The enteropathy, which can occur from the acute phase of the infection through advanced disease, involves diarrhea, increased GI inflammation, increased intestinal permeability, and malabsorption (42, 43).

Histologically, the enteropathy involves inflammatory infiltrates of lymphocytes and damage to the GI epithelial layer, including villous atrophy, crypt hyperplasia, and villous blunting (44). Importantly, these pathological changes occur in the absence of detectable bacterial, viral, or fungal enteropathogens (44). SIV-infected rhesus macaques also manifest enteropathy (45), which may be in part attributed to virus-mediated enterocyte apoptosis and occurs very early in the acute phase of infection (46). Investigators have recently reported a preferential loss from the GI tract of a subset of T cells that are defined by their secretion of the cytokine IL-17 (47, 48). These Th17 cells are thought to be critical in the defense against bacteria and fungi, particularly at mucosal surfaces, and also contribute to the homeostasis of enterocytes. Importantly, although this loss is observed in HIV infection and pathogenic SIV infection of rhesus macaques [wherein it correlates with progression to AIDS (48)], it is not observed in...
Nonpathogenic SIV infection of sooty mangabeys.

Thus, it has become apparent that the GI mucosal barrier suffers a serious immunological and structural insult very early in HIV and pathogenic SIV infection and that this damage may impair the barrier function of the gut in the defense against luminal microbes. In fact, it has long been known that damage to the barrier function of the GI tract, as occurs in inflammatory bowel disease and after chemo/radiotherapy for hematopoietic cell transplantation, results in the microbial translocation of products such as lipopolysaccharide (LPS), which correlates with systemic immune activation (49–51). Recent studies have shown that chronically HIV-infected individuals have significantly increased levels of plasma LPS compared to uninfected individuals (52). The increased levels of LPS are commensurate with levels capable of inducing an acute-phase inflammatory response (53). They are associated with increased levels of soluble CD14 and LPS binding protein, as well as decreased levels of antibodies directed against LPS core antigen, indicating bioactivity of LPS in vivo. Moreover, LPS levels are associated with both the frequency of activated memory CD8 T cells and plasma levels of the proinflammatory cytokine IFNα. Importantly, neither of these measures of activation could be directly attributed to LPS. These findings suggest that plasma LPS, in addition to its potent immunostimulatory activity through Toll-like receptor 4 (TLR-4), is also an indicator of the translocation of additional microbial products that stimulate the immune system through other receptors. Notably, in those elite controllers whose disease course progresses, the degree of CD4 T cell depletion is closely associated with the level of T cell activation, which is, in turn, associated with significantly raised levels of plasma LPS (3). These findings implicate microbial translocation as a cause of immune activation in chronically HIV-infected individuals, thus providing a direct link between the damage to the GI tract during the acute phase of infection and progression to immunodeficiency.

Depletion of GI tract CD4 T cells alone is clearly not sufficient to result in mucosal translocation and immune activation. Although pathogenic SIV infection of rhesus macaques is also associated with microbial translocation and immune activation, recent studies have shown that African green monkeys (30) and sooty mangabeys (29), both natural hosts for SIV, lose a significant fraction of their GI tract CD4 T cells during acute SIV infection yet typically have low levels of immune activation and plasma LPS even in the presence of high viral loads, and do not progress to AIDS (29,30,52). Importantly, both species manifest significant immune activation in the acute phase (28–30), with measurable microbial translocation in sooty mangabeys (29), but the immune activation and microbial translocation are transient and are controlled as the infected animals enter the chronic phase. These observations suggest that natural host species may have evolved immunological mechanisms for control of mucosal pathogens that are less dependent on CD4 T cells and may also be able to attenuate potentially harmful inflammatory responses in the face of ongoing viral replication.

Thus, in HIV and pathogenic SIV infection the GI tract is a site of massive CD4 T cell depletion, viral infection, enterocyte apoptosis, and structural damage to the epithelial surface. New therapies might aim to prevent or reduce the propagation of HIV at mucosal surfaces and to restore the immunological and epithelial integrity of the mucosal barrier, thereby circumventing the associated immune activation and disease progression (54). However, with such emphasis on immune activation as a cause of disease progression, and on the attenuation of immune activation in chronic nonpathogenic SIV infection even in the presence of high viral loads, it should not be concluded that the virus plays a minor role in disease progression in pathogenic infection. On the contrary, it plays a central role at all stages of disease (Figure 1); the relationship between immune activation and HIV may not always be direct, but clearly without the virus there is no immune activation. The efficacy of ART in
reducing immune activation bears witness to this contention.

**T CELL FUNCTION IN HIV PATHOGENESIS**

Subsets of T cells can be defined by their specificity, surface phenotype, degree of maturation, location, or functions they express upon stimulation, and any or all of these parameters can be affected by HIV infection. Which of these changes are a cause, and which a consequence, of HIV infection has been the focus of intense study for many years. Gross changes in the representation of different T cell subsets have been described (55). Besides the loss of CD4 T cells, a destruction consequential to the infection of this subset by the virus, general patterns were seen that are true of all T cells, including CD8 and gamma-delta subsets. In general, untreated individuals show a progressive loss of resting subsets (with a preferential loss of resting naive T cells during chronic disease) and elevated levels of activated T cells—for example, those expressing HLA-DR and CD38. Seminal studies by Giorgi and colleagues showed that these activated phenotypes of CD8 T cells were reasonably predictive of subsequent progression rates; high expression of CD38 was associated with a poor prognosis, whereas HLA-DR expression in the absence of CD38 was favorable (4).

Further studies showed that ART reversed, at least to some extent, many (but not all) of the changes described in chronic HIV infection (56–60). Structured treatment interruptions (STI trials) showed that these reversals were only temporary, suggesting that the remodeling of the T cell compartment accompanying HIV infection was largely a consequence of high viral loads and that therapeutic control of virus would allow the immune system to partially recover. In general, the substantial phenotypic changes described for CD4 and CD8 T cells during HIV disease rarely correlate with disease progression and are probably more indicative of an immune system under stress.

With the advent of assays to identify antigen-specific T cells (intracellular cytokine staining, or ICS), attention shifted to characterizing those cells actively involved in controlling the virus, i.e., HIV-specific CD4 and CD8 T cells. ICS can enumerate the fraction (or absolute number) of T cells that make one or more functional responses to stimulation with antigen; this is referred to as the magnitude of the response. In addition, by considering the types of different responses that are elicited by the stimulation, the quality of the response may be defined (61).

A number of studies demonstrate that the magnitude of the CD8 T cell response to HIV does not correlate with or predict progression (62, 63). Indeed, the magnitude of this response is largely correlated with viral load; successful control of viremia leads to a diminution of the T cell response (64–66). The failure to find a correlation between the CD8 T cell response...
Figure 2

Functionally defined T cell differentiation and HIV disease progression. T cell stages can be defined either by phenotype (as naive, central memory, effector memory, or terminal effector cells) or by function (expression of cytokines, chemokines, or other activities immediately following antigenic stimulation). Clinically defined correlates of progression in HIV disease have been associated with T cell functions: Better clinical outcome is associated with a prevalence of polyfunctional T cells. These cells are highly optimized for effector function by expressing multiple functions simultaneously as well as expressing high levels of cytokines on a per-cell basis. In contrast, there is little correlation between clinical outcome and the phenotype of antigen-specific cells, likely because of the broad overlaps between phenotypically defined subsets and function.

**Polyfunctional T cells**: individual antigen-specific T cells that respond to cognate antigen by exhibiting more than one or two functions simultaneously, e.g., they simultaneously make IL-2, IFNγ, and TNF.

T cells was born. When clinically defined progressors and nonprogressors were compared, a substantial difference in the quality of the HIV-specific response was apparent. In nonprogressors, a much larger fraction of the response comprised polyfunctional T cells. Indeed, even within the progressor cohort, there was a correlation between the level of polyfunctionality and viral load—a correlation that had never before been seen with any functional measurement. This has been confirmed by other studies (68, 72–74).

Recent studies in HIV-2-infected adults provide additional support for the role of functionally, as opposed to phenotypically, defined T cell subsets in viral control (75, 76). HIV-2 is typically a far less pathogenic infection than HIV-1, so far more CD4 T cells are preserved, enabling a detailed analysis of HIV-2-specific CD4 and CD8 T cells. HIV-2-specific T cells were found to be more polyfunctional, akin to the HIV-1-specific T cells in nonprogressors. Remarkably, the phenotypes of the antigen-specific T cells showed no correlation to virus and pathogenesis came as a disappointment; there was every expectation that a vigorous T cell response to the virus would be associated with better control and clinical outcome.

Nonetheless, over the past few years it has become clear that the quality, if not the magnitude, of the T cell response may provide such a correlate. Initially, studies quantified the fractions of T cells that made IFNγ, IL-2, or both on a cell-by-cell basis. Although there was no difference between progressors and nonprogressors in terms of the magnitude of the IFNγ response, the fraction of the cells that made IL-2 (alone or in combination with IFNγ) was elevated in nonprogressors (67–70). In other words, the quality of the response varied from an IFNγ-dominated response (in progressors) to a more balanced, IL-2-producing response (in nonprogressors) (Figure 2).

A seminal paper by Betts et al. dramatically extended this paradigm (71). In this study, T cell quality was defined by the independent measurement of five different functions on a cell-by-cell basis; the concept of polyfunctional
with function. Indeed, the only associations found were that more differentiated subsets produced less IL-2 and more MIP1β. There was no association between differentiation stage (defined phenotypically) and IFNγ, TNF, or degranulation.

A number of studies have found evidence of a larger role for polyfunctional T cells. Indeed, these cells appear to be relevant even in primary infection: Patients with improved resolution of viral load had more polyfunctional responses (73, 77). Even within a single individual’s response, there is heterogeneity that follows this pattern. Responses to different HIV epitopes can be individually characterized; those epitopes that induced more polyfunctional responses also induced proliferative responses, in contrast to epitopes that induced only IFNγ production (69). Heterogeneity also exists at the level of anatomical location: It appears that mucosal responses are more polyfunctional than those found in the blood. Rectal T cell responses were mildly more polyfunctional (78), while T cell responses obtained from bronchoalveolar lavage (BAL) were far more polyfunctional (35). Interestingly, the BAL shows a far better preservation of CD4 T cells than the blood of these same individuals, indicating that pathogenesis is anatomically distinct and correlates with the degree of polyfunctionality of the compartment.

Numerous studies now show that a higher level of T cells capable of IL-2 production, which are more likely to be polyfunctional T cells, is associated with better outcome in HIV disease. However, to date, these studies leave open the question of cause versus effect. Polyfunctionality did not immediately increase in progressors undergoing ART (70, 71); however, long-term changes have not been well-defined. Nonetheless, there are good reasons to believe that polyfunctional T cell responses are superior and can directly lead to better control of virus. First, in an animal model, vaccine-elicited polyfunctional CD4 T cells were far better at providing protection against challenge with *L. major*; indeed, the same number (magnitude) of monofunctional T cells provided essentially no protection (79). Second, each polyfunctional cell by definition elicits a wider repertoire of functions, both measured and unmeasured (e.g., greater expression of CD40L, required for licensing dendritic cells) (68). Third, each polyfunctional T cell produces as much as tenfold the amount of each cytokine produced by a monofunctional T cell, bringing to bear a far larger effector response directly at the effector site (76, 79, 80). Finally, through the production of IL-2, these cells are better equipped to proliferate and extend the response. In summary, polyfunctional T cells appear to be optimized effector cells that are also in the pivotal differentiation stage between central and effector memory T cells (61).

### PD-1 AND T CELL DYSFUNCTION IN HIV

Despite evidence that HIV- and SIV-specific CD8 T cells (CTLs) are involved in the control of viral replication (81–83), they have intrinsic functional defects—including decreased cytokine production, decreased proliferation, lack of polyfunctionality (described above), and lack of full effector differentiation—which could at least partially explain their failure to clear the infection fully (84, 85). Similar defects in SIV-specific CTLs also exist (86, 87). Although chronic high-level antigen stimulation is associated with the generation of many of these defects, it is unclear if there is a central unifying mechanism that regulates all these functions, or whether the different defects, while all resulting from chronic antigen stimulation, are regulated through different pathways. Multiple surface molecules can transmit both positive and negative regulatory signals to T cells, any of which could be responsible for some or all of the observed defects in HIV-specific T cells (88).

Programmed death–1 (PD-1) has recently been identified as a crucial negative regulator of T cell function in HIV infection. PD-1 is a member of the CD28 family and was originally identified as a surface receptor involved in the apoptosis of cancer cells (89, 90). The role of
PD-1 in regulating T cell function in chronic viral infection was first recognized in studies of mice with chronic lymphocytic choriomeningitis virus (LCMV) infection, which results in CTL exhaustion similar to the defects seen in HIV infection. In an elegant study, recovery from exhaustion of LCMV-specific CTLs was accomplished in vivo by blocking the interaction between PD-1 and its ligand PD-L1 (91). This recovery of T cell function occurred even in CD4-depleted mice, making the findings relevant to HIV infection. The encouraging findings led to a flurry of activity to determine the role of PD-1 in T cell exhaustion in HIV infection (e.g., 92–94).

Nearly simultaneous publications by three groups of investigators showed that PD-1 was highly expressed on HIV-specific CTLs, and that CTLs specific for less chronic or acute viruses had lower expression of PD-1. Trautmann et al. and Day et al. found a direct relationship between viral load and PD-1 expression on HIV-specific CTLs (92, 94), and Zhang et al. showed that long-term nonprogressors have HIV-specific CTLs with lower expression of PD-1 than progressors (95). All three groups showed that proliferation of virus-specific CTLs could be improved by blocking the interaction of PD-1 with PD-L1 during antigen stimulation. However, there are some discrepancies in the literature over which CTL functions are directly controlled by PD-1. Whereas some studies have linked expression of PD-1 on CTLs to impaired production of cytokines (91, 92, 94), others have emphasized the predominant role of this receptor in regulating the survival of these cells (93, 96–99). Specifically, although blocking PD-1 increases the number of HIV-specific CTLs that make cytokine in a multi-day assay, it is unclear if this is secondary to a direct effect of PD-1 on cytokine expression, or a reflection of the better proliferation/survival of HIV-specific CTLs over the course of the assay. Petrovas et al. were unable to demonstrate a direct effect of PD-1 on cytokine expression in HIV-specific CTLs in short-term assays (93). Despite these minor differences, these findings collectively support the conclusion that PD-1 expression on HIV-specific CTLs, and its engagement by PD-L1 on antigen-presenting cells during chronic antigen stimulation, is responsible for at least some of the defects in CTL function.

What is the mechanism by which PD-1 engagement impairs CTL function? Petrovas et al. investigated the association between PD-1 expression and apoptosis and concluded that PD-1 is a primary determinant of apoptosis sensitivity in CTLs (93). Within any CTL population defined by any other set of surface markers, the PD-1+ population was always more sensitive to apoptosis than the PD-1− population. In addition, the level of PD-1 expression determined the sensitivity to apoptosis, and ligation of PD-1 was sufficient to induce apoptosis, indicating that PD-1 is not just a marker of, but a direct participant in, the apoptotic pathway. Therefore, PD-1 expression leads to a profound (but potentially reversible) survival defect.

There is evidence that chronic antigen stimulation drives the expression of PD-1. First, PD-1 expression decreases when viral replication is suppressed by ART (92, 94). Second, in both HIV and SIV infections, PD-1 expression decreases on epitope-specific CTLs once the epitope has escaped, whereas CTLs specific for epitopes that have not escaped maintain high PD-1 expression (99, 100). Therefore, the PD-1-mediated impairment in CTL function is a direct consequence of high HIV-specific antigen stimulation and not general immune activation.

PD-1 is also expressed on CD4+ T cells. HIV-specific CD4+ T cells express high levels of PD-1 compared with CMV-specific CD4+ T cells, and this expression correlates with viral load (92). As was seen with CD8+ CTLs, PD-1 blockade significantly increased CD4+ T cell proliferation in vitro, suggesting a similar impact of chronic antigen stimulation, PD-1 expression, and functional impairment in both the CD4+ and CD8+ T cell arms of the immune response to HIV (92).
These findings define PD-1 as a potential therapeutic target for restoring the functional capacity of HIV-specific CTLs (Figure 3). However, it should be appreciated that PD-1 expression attenuates potentially harmful T cell responses to many self antigens and other chronic pathogens. Because many T cells express PD-1, interventions that release all CTLs from PD-1-mediated suppression are likely to have unwanted effects. Nevertheless, initial safety and tolerability studies of a PD-1 blocking antibody have been completed in monkeys, and clinical trials in cancer patients have begun. In addition, anti-PD-1 antibodies are being tested in SIV-infected monkeys. These initial studies will provide a foundation on which decisions to move into human trials in HIV-infected subjects can be based. Use of anti-PD-1 interventions may be much easier in a vaccine setting. One could target the intervention to T cells specific for a given antigen, thereby avoiding release of harmful responses from appropriate negative regulatory control.

Although much work is needed to elucidate the mechanisms and direct impact of PD-1 on T cell function, the recent discovery of a cell surface molecule that can be manipulated to reverse crucial T cell dysfunctions in HIV infection provides a very promising lead for further therapeutic development.

SUMMARY

Because of the complexity of the interactions between HIV and the immune system, many differing and often competing hypotheses of how HIV causes AIDS have been put forth. In order to avoid emulating a group of blind men describing an elephant, we need to interpret specific findings within the context of multiple other findings, and take into account not only what is observed in blood, but also what occurs at multiple other sites throughout the body. When such a view is taken, some unifying conclusions can be made. Among these are that HIV is the proximate cause of AIDS and that immune activation, although it underlies the pathogenesis of ongoing viral replication, inhibition of T cell function, and impairment in immune reconstitution, only does this as a result of HIV infection. Recent data clearly demonstrate that the gut mucosal surface and the events that lead to its damage are crucial to the establishment of generalized immune activation. This activation then drives further viral replication, leading to more tissue destruction, and a vicious cycle is established. Within this context, the major antiviral T cells that would normally control viral replication are hindered first by the generalized immune activation and second by the high antigen loads and chronic T cell stimulation. This leads to T cell functional impairments that further degrade the ability of the immune response to curtail HIV replication.

There are at least two bits of good news within this depressing scenario. First, we know that potent ART, by shutting down HIV replication, leads to an often slow and incomplete but eventual return of the immune system toward normality. Second, many of the processes...
described in this review are potential targets for new therapeutic or vaccine interventions. Although there is still much to learn, a better understanding of how HIV causes AIDS will ultimately translate into better treatment options for HIV-infected people.

DISCLOSURE STATEMENT

The authors are not aware of any biases that might be perceived as affecting the objectivity of this review.

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