

# Developments in Basic Science Research

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*Basic science research constitutes a steadily increasing part of the Conference on Retroviruses and Opportunistic Infections, and the 12th conference arguably had the strongest showing of basic science research. Presentations on cellular defense factors dominated the basic science category, and some of the presentations provided a few surprises with regard to the mechanism by which the cellular defense factor APOBEC counteracts HIV-1 infection. A second cellular defense factor has been identified in the past year and a number of presentations focused on its mode of action. Similarly, evidence for new cellular factors that positively promote viral replication were presented. Novel findings relating to viral pathogenesis were featured at the meeting and some clarity was brought to the issue of the underlying role of viral pathogenicity and immune activation in lymphocyte depletion. The crystal structure of an unliganded SIV envelope was presented and has broad significance in terms of understanding viral infection and generating better immunogens for vaccines.*

## Cellular Defense Factors

The initial discovery by the Malim laboratory<sup>1</sup> of the cellular defense protein APOBEC highlights the conflict that exists between viruses and their host at the cellular level. Before the identification of APOBEC, the cellular and humoral arms of the immune system were thought to be the major host defenses against infections by viruses such as HIV-1. Since the discovery of APOBEC and more recently, the discovery of another cellular restriction (TRIM 5 $\alpha$ ) by the Sodroski research group,<sup>2</sup> it is now becoming apparent that cellular defenses exhibit antiviral activities that oppose viral replication far more effectively than the immune system. As such, viruses have had to evolve mechanisms that allow them to circumvent these defenses so that they can replicate in monkey and human hosts. Although APOBEC was identified 3 years ago, how it blocks viral infection and how the virus defends itself from this restriction is still generating surprises. APOBEC is a cytidine deaminase that converts cytosines within the minus strand of the viral cDNA to uracils. When replicated, this results in G-to-A hypermutations in

the plus strand of the cDNA. This conversion is so severe that the viral cDNA loses its integrity both in terms of stability and in terms of its ability to encode functional viral proteins.<sup>3</sup>

Given the presence of this potent cellular defense protein, why do people get infected? The answer is that the virus has evolved a countermeasure, namely the Vif protein, the function of which is to remove APOBEC from the cell by dragging it to the proteasome, where it is degraded. To exert antiviral activity, APOBEC must be packaged within virus particles in order to subsequently influence the reverse transcription step in newly infected cells, since the expression of Vif in target cells does not ameliorate the antiviral effects of APOBEC. Until recently, the antiviral activity of APOBEC was thought to be a consequence of its enzymatic activity and that Vif was efficient in clearing the way for viral replication by depleting APOBEC from the cell and preventing its incorporation into newly budded virions. Results presented at the conference challenged these views, and it now appears that APOBEC may have antiviral activity that is independent of cytidine deaminase. This cytidine deaminase-independent antiviral activity may be active against a variety of viruses unrelated to primary lentiviruses and, in addition, the Vif countermeasure may be imperfect given the frequent presence of G-to-A hypermutations in viruses sequenced directly from patient specimens.

In his Bernard Fields Memorial lecture, Malim (Abstract 5) presented evidence that APOBEC 3G mutants that lack cytidine deaminase activity are nonetheless capable of inhibiting HIV-1 replication. There are at least 11 APOBEC-related cytosine deaminases in the human genome. APOBEC 3G and APOBEC 3F have thus far been shown to inhibit HIV-1 replication. In addition, these APOBEC proteins are expressed in cells relevant to HIV-1 replication, namely lymphocytes and macrophages. APOBEC protein family members contain consensus cytidine deaminase motifs, and specific residues that are important for zinc coordination and proton transfer, which are crucial to enzymatic activity, have been identified. APOBEC 3G contains 2 such cytidine deaminase motifs. Malim presented evidence that only the C-terminal active site was necessary for the DNA-mutating activity of APOBEC 3C. Nevertheless, APOBEC 3G lacking this C-terminal active site potently suppressed HIV-1 infection without inducing G-to-A hypermutation. Although the mechanism through which APOBEC 3G suppresses HIV-1 infection independently of cytidine deaminase activity remains to be determined, this antiviral activity appears to require the packaging of APOBEC proteins into virions. As such, Vif is still important in order to inhibit the cytidine deaminase-independent antiviral activities of APOBEC.

There were more surprises regarding the antiviral activity of APOBEC in one study (Abstract 30). The study, conducted by the Green research group, originally set out to determine why cytoplasmic APOBEC is not active against incoming virions. APOBEC 3G was found to exist in a high molecular weight ribonucleoprotein complex that does not contain cytidine deaminase activity. When this complex was treated with RNAase, it was converted to a low molecular weight complex that exhibited cytidine deaminase activity. The investigators then looked at the form in which APOBEC 3G exists in resting CD4+ T lymphocytes and in primary undifferen-

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tiated monocytes. These cells have long been known to be refractory to HIV-1 infection, and an important question in the field regards the nature of the block that exists in these cells. Surprisingly, APOBEC 3G in resting lymphocytes and monocytes was present in a low molecular weight complex, which was subsequently converted to a high molecular weight complex when resting lymphocytes were activated or when monocytes were induced to differentiate into macrophages. The investigators then used the technique of RNA interference to modulate the expression of APOBEC 3G in resting lymphocytes. When small interfering RNAase specific for APOBEC 3G were introduced into resting cells, the block to HIV-1 infection was relieved. This may shed light on the mechanism by which HIV-1 infection is restricted in resting lymphocytes and in monocytes. It remains to be determined whether the mechanism by which the low molecular weight APOBEC complex in resting cells blocks HIV-1 infection is analogous to the mechanism by which cytidine deaminase-deficient mutants of APOBEC 3G block HIV-1 infection.

Continuing the theme of the mechanism by which APOBEC modulates HIV-1 infection, another study (Abstract 241) characterized which APOBEC 3 family members influence HIV-1 infection. There are 7 APOBEC 3 genes (A3A through A3G). A3B, in addition to A3F and A3G, exhibited antiviral activity and were specifically packaged into virions. Surprisingly, A3F and A3G were suppressed by HIV-1 Vif, but A3B was not. The caveat to this study is that A3B does not appear to be expressed in tissues relevant to HIV-1 infection and as such may not be able to influence viral replication *in vivo*.

Studies attempting to gain insight into the mechanism by which Vif blocks the antiviral activity of APOBEC were also featured at the conference. Two (Abstracts 31, 32) presented some of the cellular factors that are involved in Vif-mediated targeting of APOBEC to the proteasome. It is now becoming clear that HIV-1 harbors a suppressor of cytokine signaling (SOCS)-box-like motif that mediates interaction with an E3 ligase complex that is ultimately targeted to proteasome. This information could be valuable in terms of designing small-molecule inhibitors that prevent

Vif from interacting with the E3 ubiquitin ligase complex, since this would prevent APOBEC degradation and allow it to exert antiviral activity even in the presence of Vif.

It is clear that the Vif protein of primate lentiviruses has evolved to potentially suppress the antiviral activity of APOBEC, but there is accumulating evidence that the ability of Vif to counteract APOBEC is not absolute and as such, viral genomes are influenced by APOBEC proteins. The number of G-to-A hypermutations in viral plus-strand cDNA in the presence of Vif is higher than in cells that do not express APOBEC 3G (Abstract 5). Therefore, even in the presence of Vif, APOBEC 3G is still able to effect hypermutation of viral cDNA. Another study (Abstract 29) presented evidence that the virus may have an additional mechanism to further reduce the effects of APOBEC that escapes Vif-mediated degradation. Within cells, DNA repair enzymes such as uracil DNA glycosylase (UDG) prevent misincorporation of uracil into DNA by targeting hypermutated transcripts for degradation. UDG has previously been shown to bind to the accessory protein Vpr of HIV-1, although the functional significance of this interaction is not clear.

Schröfelbauer and colleagues (Abstract 29) demonstrated that HIV-1 Vpr, through its interaction with UDG, limits C-U deamination by APOBEC 3 so as to increase the fidelity of viral reverse transcription. These data illustrate that primate lentiviruses have gone to extraordinary measures to limit susceptibility to cytidine deaminase imposed by APOBEC. Continuing this theme, a study by Bourara and colleagues (Abstract 236) presented evidence that the hypermutational activity of APOBEC 3 on viral cDNA may facilitate viral evolution *in vivo*. Primate lentiviruses rapidly evolve and, as a result, can adapt to changes in the environment as imposed, for example, by antiviral pressure or immune surveillance. Traditionally, the ability of HIV-1 to evolve is principally considered to be a result of error-prone reverse transcription. However, by direct sequencing of viral sequences in clinical specimens, it is clear that there is an overrepresentation of G-to-A mutations in viral genomes. As such, these could contribute to accelerated viral evolution

and may assist in allowing the virus to rapidly evolve drug resistance or escape from cytotoxic T cells or neutralizing antibodies.

Adding to the excitement in the field generated by the discovery of the defense factor APOBEC 3G was the discovery in the past year of a second cellular defense called TRIM 5 $\alpha$  by Sodroski's laboratory. As expected, research on the mechanism by which TRIM 5 $\alpha$  opposes viral replication was well represented at the conference (Abstracts 34, 152LB, 174, 175, 231, 234). A central feature of retroviruses and primate lentiviruses regards their host-species specificity, as illustrated by the fact that these viruses frequently encounter early blocks to infection after entering cells from different species. For example, HIV-1 does not efficiently infect monkey cells, and with the discovery of TRIM 5 $\alpha$ , part of the mechanism by which monkey cells restrict HIV-1 infection is becoming clearer. Research from a number of groups had established that HIV infection of monkey cells is impaired early after infection to the extent that there is very little reverse transcription in these cells. Therefore, it was suspected that cellular proteins in these monkey cells were impairing an early step such as HIV-1 uncoating. To identify the factor responsible, the Sodroski group expressed a monkey cDNA library in human cells and then challenged those cells with an HIV-1 variant that carries a fluorescent marker. They then identified the genes that were expressed in cells that resisted HIV infection (and that presumably expressed the monkey restriction factor). This strategy led to the identification of TRIM 5 $\alpha$ .

The details by which this protein blocks HIV-1 infection are still being worked out, but it is believed that TRIM 5 $\alpha$  targets the viral capsid to interfere with uncoating of the viral core and release of genomic viral RNA following infection. TRIM 5 $\alpha$  belongs to a family of proteins defined by a tripartite motif consisting of RING, B-box 2, and coiled-coil domains. The TRIM 5 $\alpha$  contains a C-terminal B30.2 (SPRY) domain and within this domain are variable regions that differ depending upon the species of origin. Research presented at the meeting (Abstract 34) has shed light on why monkey but not human TRIM 5 $\alpha$  blocks HIV-1 infection. When only 3 amino acids

within the first variable region of the human TRIM 5 $\alpha$  B30.2 domain were altered to resemble monkey TRIM 5 $\alpha$ , the human chimeric TRIM 5 $\alpha$ , which still was more than 98% identical to the human protein, potently suppressed HIV-1 infection. Correspondingly, a single amino-acid change in this region of human TRIM 5 $\alpha$  resulted in a protein that potently restricted SIV infection. These studies demonstrate the potent effect of host genetics on viral replication and, further, how cellular defense factors have shaped viral genomes. The hope is that this information will ultimately provide the rationale for novel therapeutics that may accentuate the ability of human TRIM 5 $\alpha$  to interact with HIV-1 capsid and block viral replication.

A number of groups previously demonstrated that the species-specific restriction to HIV-1 infection could be modulated by a cellular protein called cyclophilin A. It is now clear that cyclophilin A is required for TRIM 5 $\alpha$ -mediated restriction of HIV-1 in cells from Old World monkeys (Abstracts 175, 231, 232). Cyclophilin A is a peptidyl-prolyl isomerase first identified through its ability to interact with HIV-1 capsid. Studies in which cyclophilin A was inhibited by RNAase interference or was knocked out by gene deletion revealed that although cyclophilin A is packaged within virions through its interactions with the viral capsid, cyclophilin A in the target cells and not in the producer cell modulates viral infectivity, such that in the absence of cyclophilin A, viral replication is enhanced in cells that manifest TRIM 5 $\alpha$  restriction.

Vpu is an accessory protein that is specific to HIV-1 and a few SIV variants. The role of Vpu in HIV-1 replication is not fully understood. Its previously reported activities include enhancement of viral particle release and cooperation with the viral envelope glycoprotein to downregulate CD4 from the cell surface. Studies presented at the meeting (Abstract 178) suggest that Vpu overcomes a dominant restriction to virus assembly that exists specifically in human cells. Thus, in heterokaryons formed between human and African Green monkey cells, HIV-1 assembly was inefficient and Vpu enhanced assembly. The human protein that inhibits viral assembly and that is targeted by Vpu awaits identification.

## Positive Cellular Cofactors

On the flip side of cellular factors that oppose viral replication were presentations dealing with cellular factors that promote viral replication. Over the past 2 to 3 years, perhaps the greatest understanding regarding the cellular machinery that drives distinct steps in the viral replication cycle have dealt with the viral-budding step. During the process of virus budding, a membrane fission event allows the fully assembled virion to detach from the plasma membrane of the host cell. Cellular factors that are required for this fission event were discussed in 2 studies presented (Abstracts 176, 177). Some of the cellular factors that participate in virion budding also play an important role in membrane invagination events that are required for detachment of a phagocytic vacuole from the plasma membrane or for formation of multivesicular bodies that are involved in trafficking of processed antigens through the cell (Abstract 116). The identification of critical interactions between structural Gag proteins of the virus and cellular proteins involved in vacuolar biogenesis points to novel targets for therapeutic infection.

Cellular factors that may play a role in orienting the virus within the cell prior to integration were also presented at the meeting (Abstract 35). Arguably, the least-understood aspect of HIV-1 replication regards factors that aid in its translocation from the point of entry at the cell membrane to cellular DNA within the nucleus. To put this into perspective, if one considers a cell the size of a football field, the viral cDNA with its associated viral proteins (for example, reverse transcriptase and integrase) would be the size of a football. Therefore, there has been suspicion that the virus may use a roadmap in order to ensure that it follows the appropriate route to the center of the cell. Some data (Abstract 35) indicated that proteins of the inner nuclear envelope may be used by HIV-1 as part of this roadmap. Evidence was presented that the nuclear envelope itself is required for efficient HIV-1 infection but not for infection by other retroviruses such as murine leukemia virus (MLV). RNA interference was used to silence the expression of a number of inner nuclear envelope proteins. Silencing of 2 nuclear envelope

proteins, namely barrier-to-autointegration factor (BAF) and emerlin, did not interfere with the ability of the virus to localize the nucleus, but specifically interfered with the ability of the virus to integrate. Inefficient integration was accompanied by an increased formation of episomal cDNA, which are dead end products of viral infection to the point that almost all viral cDNAs in the nucleus were in the form of nonfunctional episomes. A similar effect is seen when infection is blocked by small-molecule inhibitors of the integration step. The authors propose that the inner nuclear envelope facilitates the interaction of incoming viral cDNA with cellular chromatin in order to prevent inactivation of the viral cDNA by recombinases and ligases within the nucleus that promote the circularization of viral cDNA. The study also suggests that HIV-1 replication may be restricted to nondividing cells.

RNA interference is widely exploited as a tool to regulate gene expression. As such, it offers a valuable approach to validating cellular cofactors of HIV-1 replication, since one can silence the expression of individual cellular genes and gauge whether, in the absence of that gene, viral replication is affected. Even so, it is becoming clear that HIV-1 cofactor validation is not trivial. A poster discussion session (Abstracts 220-227) was devoted to making sense of the role of LEDGF in HIV-1 replication. LEDGF is a transcriptional coactivator that was found to interact with lentiviral integrases in mammalian cells and was suggested to act as a cofactor for viral integration. However, the field has been unable to reach a consensus on whether LEDGF is a bona fide cofactor for viral integration. Silencing LEDGF by RNA interference has produced conflicting results ranging from a large impact on viral infection to negligible impact, even though biochemical data convincingly demonstrate that LEDGF tightly interacts with the viral integrase in mammalian cells. The take-home message is that the LEDGF-integrase association may be required in a viral context that is not reproduced with *in vitro* replication assays. For example, data from the Bushman laboratory indicate that HIV-1 preferentially integrates into active cellular genes (Abstract 251). Although the underlying mechanism by which HIV

favors particular integration sites over others is not understood, one possibility is that components of the viral preintegration complex, such as LEDGF, may play a role in integration site selection. If this is the case, the absence of LEDGF may not result in measurable differences in viral replication in simple in vitro culture systems.

Some presentations (Abstracts 257, 259, 260, 261) were aimed at understanding the factors that differentially influence endosomal versus plasma membrane budding of HIV-1. It has been previously demonstrated that in cells such as macrophages, viruses bud more selectively at cytoplasmic membranes than at the plasma membrane. These studies underscore the notion that endosomal assembly of HIV-1 may be a regulated process that HIV-1 has evolved to exploit. It remains to be determined whether intracellular budding of HIV-1 offers a survival advantage by, for example, providing a compartment in which virions evade immune surveillance.

Studies describing the structure of an unliganded SIV envelope (Abstracts 7, 28) generated a lot of interest. The structure of the core domain of HIV-1 gp120 in a CD4-bound conformation has previously been described. Now, with the structural characterization of the core of a CD4-nonbound SIV gp120, a better understanding of the conformational changes imposed by receptor binding can be revealed. In the case of HIV-1, envelope binding to CD4 causes a major conformational change that exposes coreceptor binding domains in the protein. This may be a mechanism that HIV-1 has adopted in order to protect coreceptor binding domains from recognition by the host antibody response so that these domains are exposed immediately prior to coreceptor contact. Therefore, structural characterization of CD4-bound and -nonbound envelope glycoproteins has important implications not only for the understanding of the viral infection process but also for the design of vaccine immunogens that induce neutralizing antibodies to sensitive coreceptor binding sites.

## Pathogenesis

A long-standing controversy in AIDS pathogenesis regards the relative roles of virus-mediated cell killing and indirect

cell killing in lymphocyte depletion. Although HIV-1 is clearly recognized as a cytopathic virus that rapidly destroys CD4+ T lymphocytes in vitro, other processes such as immune activation have been proposed to play an important role in accelerated lymphocyte turnover in vivo. One presentation (Abstract 127) reinforced the case for direct virus-mediated cytopathicity in lymphocyte depletion by pathogenic primate lentiviruses. Studies in SIV-infected monkeys previously established that the gastrointestinal tract is a principal site for viral replication. More recently, by characterizing lymphocyte subsets in the gastrointestinal tract and lymph node in acutely infected individuals, it has been observed that lymphocytes are rapidly depleted by massive viral replication, which corresponds with acute high-level viremia.

In his plenary presentation, Douek presented evidence that lymphocyte depletion is directly due to viral cytopathicity. Using polymerase chain reaction (PCR) to quantitate the frequency of HIV-1 infected cells, it was demonstrated that during lymphocyte depletion in acute infection, the majority of lymphocytes harbor viral DNA. These findings, although not unexpected, have important implications for the treatment of HIV-1 infection, since the unrestricted viral replication that occurs during acute infection may be a defining event in the natural progression of disease that dictates viral set point (the steady-state level of viremia that is achieved following acute infection) and perhaps time to onset of disease. As such, it will be important to evaluate whether prophylactic or early therapeutic intervention prior to that interrupts this profound acute replication, preserves the integrity of gastrointestinal lymphocytes, and affects viral set point and time to onset of disease.

Several studies (Abstracts 152, 153, 154, 155) investigated characteristics of SIV infection in natural and nonnatural host species that might explain the differential manifestations of disease in these systems. In naturally infected monkeys such as sooty mangabeys, SIV replicates to extraordinarily high titers and promotes accelerated lymphocyte turnover. Despite this, there is no evidence for AIDS-like symptoms and the mechanism for lack of disease in these animals has been a central question in the field.

Recent studies have suggested that high-level SIV replication occurs in the absence of generalized immune activation; in pathogenic infections including HIV-1-infected humans or SIV-infected rhesus macaques, high-level viral replication is accompanied by a generalized immune activation. Staprans and colleagues (Abstract 152) presented evidence that differences in dendritic cell (DC) function may partially contribute to the differential immune activation that is seen in pathogenic and nonpathogenic primate lentivirus infections. There were marked differences in DC maturation between pathogenic and nonpathogenic infection, which was reflected by increased expression of CCR7 (which is reported to play a role in immune cell homing to lymphoid tissue). The authors propose that this leads to accumulation of mature DCs in the lymph nodes, which leads to more extensive T-cell proliferation in acutely infected rhesus macaques. The authors also noted differences in the response of rhesus and sooty mangabey DCs to CpG and to activation by SIV. Collectively, these results suggest that DC responsiveness may play an important role in determining the magnitude of the inflammatory response that ultimately plays a role in bystander cell damage characteristic of pathogenic lentivirus infection.

The relationship between host-cell activation and susceptibility to HIV-1 infection is a well-recognized feature of primate lentivirus replication. Quiescent lymphocytes are refractory to infection and, upon entry into cell cycle (G1 phase and beyond), these cells acquire susceptibility to infection. As a result, factors that affect the cell-cycle state of CD4+ lymphocytes can directly affect the extent of viral replication. Both macrophages and lymphocytes have previously been reported to provide signals in trans that promote the ability of neighboring lymphocytes to replicate HIV-1. Dendritic cells capture virions and transmit capture virions to neighboring T cells while at the same time providing a signal that induces those cells to go into cell cycle. Infected macrophages produce virions and soluble factors that increase susceptibility of neighboring lymphocytes to infection by virions released from the infected macrophages. In an extension of this theme, one study (Abstract 148) demon-

strated that CD16+ monocytes, which are refractory to productive HIV-1 infection, can nevertheless transmit HIV-1 to T cells in trans and at the same time release soluble factors that increase their susceptibility to infection. The authors demonstrated that CD16+ monocytes more efficiently capture and transmit virions to activated CD4+ T cells during cell-cell contact and release eotaxin-2 and MCP-1, which activate resting CD4+ T cells, thereby rendering them permissive to viral infection.

One issue that has attracted the interest of a number of groups is whether the HIV-1 envelope, upon engaging receptor and core receptor molecules, can engender signals that influence susceptibility of the cell to infection. In support of this, Balabanian and colleagues (Abstract 200) presented evidence that the viral envelope glycoprotein exhibits similar signaling characteristics to the CXCR4 ligand SDF-1. The authors demonstrated that a CXCR4-tropic gp120, when added to primary CD4+ T cells, induced calcium mobilization and activation of PI3K and MAP kinases, as well as actin cytoskeleton rearrangements and membrane ruffling. Importantly, these effects were also mediated by inactivated HIV-1 virions containing conformationally intact envelope glycoproteins. The authors propose that envelope may mimic the action of chemokines such as SDF1 so as to promote the recruitment of target cells and, through the cytoskeleton effects, facilitate the uptake of viruses by target cells. In a similar vein, another presentation (Abstract 279) demonstrated that HIV-1 gp120 can elicit release of tumor necrosis factor (TNF)- $\alpha$  by human macrophages and that this stimulation is CCR5 dependent and mediated through a PI3 kinase- and MAPK kinase-dependent signaling pathway. The authors propose that induction of TNF- $\alpha$  in this way may play a role in processes such as AIDS-related dementia in which HIV-1-infect-

ed microglia have been reported to induce neuronal dysfunction through the release of soluble neurotoxins. One study (Abstract 278) suggested that CCR5 signaling by R5-tropic virions increases the efficiency of the viral replication upon infection. Another (Abstract 146) presented evidence that variation in gene copy number of CCL3L1, an agonist of the viral core receptor CCR5, influenced susceptibility to HIV-1 infection. Of note, CCL3L1 copy number was only important in the context of CCR5 genotype such that low CCL3L1 copy number combined with specific CCR5 (detrimental) genotypes were associated with 4-fold differences in the risk of acquiring HIV in the context of vertical transmission.

Swingler and colleagues (Abstract 149) demonstrated that soluble factors released by HIV-1-infected macrophages not only influence CD4+ lymphocyte function but can also directly impact B lymphocyte proliferation and differentiation. The authors presented evidence that the viral *nef* gene induces release of ferritin light chain, a protein with roles in iron metabolism, and that L-ferritin induces B-cell proliferation and differentiation to immunoglobulin-secreting plasma cells. The authors further demonstrated a direct correlation between plasma ferritin levels in HIV-1-infected individuals exhibiting hypergammaglobulinemia but not in SIV-infected monkeys that do not exhibit hypergammaglobulinemia. This correlated with the differential ability of HIV and SIV *nef* to induce ferritin from infected macrophages in vitro. Hypergammaglobulinemia is a well-recognized but poorly understood manifestation of HIV-1 infection. The authors propose that B-cell dysfunctions in AIDS may be attributable to the action of the viral Nef protein in infected macrophages.

*Financial Disclosure: Dr Stevenson has no financial affiliations with commercial organizations that may have interests related to the content of this article.*

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*Top HIV Med*. 2005;13(1):4-8  
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