Immune activation and collateral damage in AIDS pathogenesis

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In the past decade, evidence has accumulated that human immunodeficiency virus (HIV)-induced chronic immune activation drives progression to AIDS. Studies among different monkey species have shown that the difference between pathological and non-pathological infection is determined by the response of the immune system to the virus, rather than its cytopathicity. Here we review the current understanding of the various mechanisms driving chronic immune activation in HIV infection, the cell types involved, its effects on HIV-specific immunity, and how persistent inflammation may cause AIDS and the wide spectrum of non-AIDS related pathology. We argue that therapeutic relief of inflammation may be beneficial to delay HIV-disease progression and to reduce non-AIDS related pathological side effects of HIV-induced chronic immune stimulation.

Keywords: AIDS, pathogenesis, immune activation, TLR, Immunity, therapy

CHRONIC IMMUNE ACTIVATION IS THE PRIMARY DRIVER IN HIV PATHOGENESIS

Upon discovery of the virus that causes AIDS, the name human immunodeficiency virus (HIV) was coined because the virus eventually causes severe immune deficiency. This was based on the clinical symptoms with which end-stage HIV-infected patients presented and on the gradual decline of CD4+ T-cell numbers in the blood, which is still considered a hallmark of HIV-disease progression. The finding that HIV is confined to CD4+ leukocytes and is cytotoxic for CD4+ T cells established the hypothesis that HIV causes immune deficiency by directly killing CD4+ T cells and impeding CD4+ T-cell renewal (1). The molecular mechanisms involved in CD4+ T-cell killing by HIV infection have been studied in great detail, leading to novel insights into the down-stream effects of abortive infection and viral integration on cell death (2–4). However, increased apoptosis rates in HIV-infected individuals are not confined to infected CD4+ T cells, but are also observed in non-infected CD4+ T cells and in cell types that are not even targets for HIV infection, suggesting that the cytopathic effects of HIV are not the full story (5, 6).

Paradoxically, HIV induces strong cellular immune responses, both with respect to magnitude and breadth (7–11), and even in progressive HIV infection, high avidity HIV-specific CD8+ T cells are being induced (12). Both CD4+ and CD8+ T cells are more activated in acute and chronic HIV infection, and hence proliferate rapidly and have a short half life. This explains why both T-cell production and death rates are increased throughout HIV infection (13, 14). At first, the high division rate of CD4+ T cells in untreated HIV-infected patients was interpreted to reflect a homeostatic response to the loss of CD4+ T cells (15–18). Studies in patients on combination anti-retroviral therapy (cART) pointed out, however, that T-cell proliferation rates drop concomitant with the loss of virus, even when CD4+ T-cell numbers are still far below healthy control levels, suggesting that the increased T-cell division rates are caused by the virus itself. It became clear that chronic immune activation is a hallmark of pathogenic HIV infection, exemplified by the increased expression of soluble and cellular immune activation markers, including IFNα, TNFα, and sTNFR and the increased fraction of activated CD8+ T cells; markers that have long been used as surrogate markers for HIV-disease progression (19–27). In fact, the level of immune activation is the best predictor of progression to AIDS (28, 29) and death (22, 30–32), independent of HIV viral load. HIV-2 infection is characterized by an overall slower progression rate, lower viral loads, and higher CD4+ T-cell numbers than HIV-1 infection (33). Yet, the cytopathicity of HIV-2 for human CD4+ lymphoid cells is not lower compared to HIV-1 (34). A striking difference between the two viral subtypes is that the level of immune activation is lower in HIV-2 compared to HIV-1 infection, although expression patterns and prognostic values for immune activation markers were found to be similar when patients with HIV-1 or HIV-2 infection were matched for CD4+ T-cell depletion levels (35, 36) These observations were paralleled by insights from simian immunodeficiency virus (SIV) infection in sooty mangabeys (SMs) and African green monkeys (AGMs). SIV infection in these animals is characterized by high viral loads without high levels of immune activation, and does not lead to AIDS, which will be discussed in detail in the Box 1 below (37, 38). Together, these observations have gradually shifted the paradigm from the classical hypothesis that viral cytopathicity is the primary driver of CD4+ T-cell depletion and immune deficiency, to the hypothesis that chronic immune activation is the cause of T-cell depletion and immune deficiency (35, 39).
Damage control in non-pathogenic SIV infection

In pathogenic SIV infection in rhesus macaques (RM), high levels of immune activation are associated with progression to AIDS. SIV infection in sooty mangabeys (SMs) and African green monkeys (AGMs), in contrast, do not lead to AIDS despite high viral loads (37, 87–91). Interestingly, SM do not mount stronger cytoytic T-cell or neutralizing antibody responses to SIV compared to RM, and productively infected CD4+ T cells in SIV-infected SM and RM have similar life spans (92–94). Several lines of evidence show that systemically LPS induces features of pathogenic SIV infection (95), that pre-existing microbial translocation and loss of GI integrity in pigtail macaques was associated with faster SIV disease progression (96). In non-pathogenic, like in pathogenic SIV infection, however, a severe depletion of memory T cells in the gut occurs, apparently without causing generalized immune activation in non-pathogenic SIV infection (64, 55).

As the dynamics of virus and virus-infected CD4+ T cells in these animal models of SIV infection are comparable, excessive indirect activation-induced killing of T cells in rhesus macaques has been proposed to be the major pathological difference (37, 38, 87, 97–100). Indeed, despite the fact that RM develop strong immune responses upon SIV infection, these responses fail to clear the virus, resulting in persistently high levels of immune activation throughout infection (38, 101).

Compelling evidence has been obtained for a SM-specific polymorphism in TLR signaling, leading to attenuated production of type I IFN by pDCs induced via TLR7/9 activation in SIV-infected SM (102, 103). The gene involved, IRF-7, is a signaling protein downstream of TLR7 and 9. Interestingly, TLR7- and 9-induced production of TNFα appeared to be unaffected in SM, which agrees with the fact that TNFα release is mediated by the NF-κB and not by the IRF-7 pathway. This observation suggests that release of type I IFNs, but not TNFα, may be critical for SIV pathogenesis, which makes IFNα and IRF-7 potential drug targets. Despite the inability of SM to produce high levels of type I IFNs upon TLR7/9 activation by SIV, peak viremia during acute SIV infection in these animals is accompanied by clear signs of an innate and adaptive immune response, including the induction of IFN-stimulated genes (ISGs) (104, 105). Gene expression profiling showed the induction of ISG, acute inflammatory genes, and genes associated with chemotaxis and neutrophil recruitment, DC activation and maturation, apoptosis, and cytoytic T-cell responses during the acute phase of both pathogenic and non-pathogenic SIV infection (63, 104–106). In SM and AGM, expression of ISGs returns to normal levels after 30 days of infection. Since this decline in inflammation is paralleled by a gene expression program of immune regulatory genes, including genes that down-regulate T-cell responses [e.g., indolamine 2,3 dioxygenase (IDO), IL10, LAG3, and PD-L1] and genes that down-regulate IFN responses (e.g., adenosine deaminase), it has been proposed that active downregulation may be involved (63, 104). Further detailed mechanistic studies are required to reveal whether – and if so which – specific down-regulatory pathways are involved. Of note, also host genes implied in intracellular viral restriction are rapidly up-regulated in non-pathogenic infection (83, 104).

If type I IFN is one of the main causes of immune activation in HIV and SIV infection, it remains puzzling how the clear difference in IFNα production by pDC from SIV-infected SM and RM can be reconciled with the apparent similarity of immune responses, and specifically the expression of IFNα-inducible genes, observed during acute SIV infection of both species. There is, however, evidence that upregulation of ISGs in acutely SIV-infected SM is induced even though IFNα production by their pDCs is severely diminished (66, 83, 104). Interestingly, Favre and colleagues (66) found upregulation of IFNα, but not IL12 and IL6, in acute SIV infection in AGM, although IFNα release was very limited in duration compared to the sustained release of all three cytokines in pathogenic SIV infection. Also the detailed characteristics of immune activation in acutely SIV-infected RM and SM are quite different. Acute SIV infection in SM (and AGM) is not accompanied by increased CD4+ T-cell turnover, but strong increases in CD8+ T-cell activation, division (Ki67 expression) and apoptosis have been observed (99, 102, 107, 108). Thus, both timing and quality of gene expression of pro-inflammatory cytokines seem to be critically different between pathogenic and non-pathogenic SIV infection (109). Taken together, current data are compatible with the idea that SM and AGM respond to SIV with a limited and transient innate response and with an adaptive response that is mainly restricted to CD8+ T cells. In pathogenic SIV infection, an excessive innate response is generated with sustained IFNα and ISG induction which induces proliferation of NK cells and a broad SIV-specific and bystander CD4+ and CD8+ T-cell response (83, 102, 108). It could be that in SM and AGM, low and transient type I IFN responses during acute SIV infection induce a different gene expression program, allowing for resolution and/or downregulation of the immune response during subsequent chronic SIV infection.

It has been proposed that damage control in SIV-infected SM may in part be due to the preservation of central memory CD4+ T cells (Tcm) which are thought to provide protection against the harmful side effects of bacterial translocation (110). Depletion of memory T cells from the gut and bacterial translocation occur only transiently during acute SIV infection in SMs (54). In contrast to rhesus macaques, SMs are able to avoid epithelial barrier breakdown and thereby limit the undesired side effects of bacterial translocation during chronic SIV infection (111). SM are able to spare Tcm from viral infection because of low CCR5 expression (112), while in AGM Tcm may be protected against SIV infection by CD4 downregulation (113). In pathogenic SIV and HIV infection, in contrast, Tcm are thought to be selectively lost through viral infection (112) However, the observation that the number of activated and naive T cells, and not the number of Tcm, is predictive for HIV-disease progression does not support the idea that Tcm numbers are most critical (114). High levels of immune activation in pathogenic SIV infection may promote SIV infection of Tcm, resulting in Tcm depletion which may contribute to the vicious cycle of loss of immune control. Further investigations are needed to better quantify the contribution of the various mechanisms that cause CD4+ Tcm activation and death.

In conclusion, non-pathogenic SIV infection of SM and AGM are examples of a pathogen-host symbiosis with an established state of tolerance. This is not immunological tolerance in the strict sense, but a state of tolerance in which the host resists the pathological effects of the virus by avoiding excessive inflammation (115, 116). Further investigation into the various and potentially different mechanisms by which SM and AGM avoid chronic immune activation is warranted and of great importance for our understanding and the treatment of HIV disease.

CAUSES OF IMMUNE ACTIVATION IN HIV INFECTION

It has long been known that innate and adaptive immunity get activated upon acute HIV infection, as extensively described and reviewed elsewhere (35, 39–46). Chronic HIV infection is now known to be characterized by increased expression of pro-inflammatory cytokines, including type I IFNs, IL-6, TGFβ, IL-8,
IL-1α, and IL-1β, serum markers of inflammation including sCD14, CRP, cystatin C, D-dimers, and activation of the coagulation system (47). In the last couple of years much attention has focused at the causes of immune activation in HIV infection, with a redirection of research focus from T-cell immunity to innate immunity.

**BREACH OF GASTRO-INTESTINAL IMMUNITY**

In the late 1990s, acute SIV infection in rhesus macaques (RMs) was shown to induce a severe and rapid depletion of memory CD4+ T cells from the gut (48). Later, in both humans and monkeys, it was found that this breach of the gut immune system resulted in a significant increase in bacterial components, including lipopolysaccharide (LPS), in the blood (49–51). LPS is a known activator of innate immune cells via Toll-like receptor (TLR) 4, and LPS concentrations in the circulation of HIV-infected individuals correlated strongly with T-cell activation levels (51, 52). It was concluded that translocation of immune stimulatory bacterial products contributes to systemic immune activation, via TLR activation of various leukocyte populations. LPS was used as an indicator for bacterial translocation, but other bacterial products, such as flagellin, peptidoglycan, and bacterial CpG-rich DNA domains that are recognized by TLR2, 5, and 9 respectively, may also contribute to immune activation. It was proposed that the early attack on the memory CD4+ T-cell population in the gut may be a critical determinant of disease progression (53). However, also in non-pathogenic SIV infection a severe depletion of memory T cells in the gut occurs, apparently without causing generalized immune activation (54, 55). Moreover, an attenuated variant of pathogenic SIVmac239 was shown to spare mucosal CD4+ T cells and yet to cause T-cell activation, CD4+ T-cell loss, and progression to AIDS without any signs of microbial translocation (56), showing that immune activation due to gut damage is not required to develop AIDS. On the other hand, in patients on cART, with very low HIV viral load, residual levels of bacterial translocation were positively correlated with immune activation and collateral damage in the course of viral infection (57–63).

The breach of gut integrity in pathogenic SIV and HIV infection has been shown to be associated with depletion of CD4+ Th17 cells, a cell type that is normally abundant in the mucosa and is known to be involved in immunity to commensal bacteria (64). It is assumed that the immune system normally keeps a delicate balance between T regulatory (Treg) cells and Th17 cells, to protect against pathogens but avoid collateral damage from excessive immune responses (65). The selective loss of Th17 CD4+ T cells from the gut – possibly due to selective infection – has therefore been held responsible for the long-term loss of the intestinal integrity and thereby for chronic immune activation in pathogenic HIV infection (64, 66, 67). More recently, depletion of IL-21-producing CD4+ T cells has been observed in both the blood and rectal mucosa of SIV-infected RMs (68). Treatment of these animals with IL-21 resulted in the maintenance of intestinal Th17 cells, and a reduction of microbial translocation and systemic inflammation (69). The dynamics of the Th17/Treg balance and the role of Th17 cells and Th17-derived cytokines in HIV infection is currently subject of intensive study.

**SINGLE-STRANDED RNA, TOLL-LIKE RECEPTORS, AND TYPE I IFN PRODUCTION**

In 2004 it was reported that TLR7 and 8 recognize RNA from various viruses (70, 71), and it has been demonstrated that single-stranded (ss) HIV RNA directly activates the innate immune system via these TLRs (72, 73). After endosomal binding of ssHIV RNA to TLR7, HIV induces the release of type I interferons by plasmacytoid dendritic cells (pDCs) through the upregulation of TRAIL (72–75). Single stranded HIV RNA has also been shown to activate NK cells in a TLR7 and 8 dependent way, and this process is dependent on cell–cell contact between pDCs and monocytes (76). Finally, pro-inflammatory responses can be induced through intracellular recognition of HIV DNA intermediates. These intermediates can be the result of abortive HIV infection of CD4+ T cells, and induce the production of IFN-β and IL-1β (4). In agreement with these *in vitro* observations, gene expression analyses of lymphocytes from HIV-infected persons were shown to have a dominant signature of IFN-stimulated genes (ISGs) (77, 78). Immediately after start of cART – when virus production and viral load rapidly decline – markers of T-cell activation, expression of pro-inflammatory cytokines such as IFNα, IL-6, IL-1-β, and macrophage inflammatory protein-1α, adhesion molecules VCAM-1 and ICAM-1, and the levels of soluble markers for endothelial cell and coagulation activation are all rapidly and strongly reduced, although not to normal levels (15, 18, 73, 79–81). These data suggest that HIV itself, most likely through its ssRNA or DNA intermediates, is an important driver of immune activation in untreated HIV infection.

Type I IFNs provide an important link between chronic innate and adaptive immune activation in HIV infection, because they induce activation and maturation of pDCs, NK cells, T cells, and B cells (82). Gene expression profile data from pathogenic and non-pathogenic SIV-infected primates suggest that persistent release of type I IFNs is a particular feature of pathogenic infection (83). It is well established that pDCs are mass producers of type I IFNs (82). At a certain point, pDCs typically become refractory to restitution by TLR ligands, thereby avoiding excessive immune activation and collateral damage in the course of viral infection (84, 85). Bhattacharya and colleagues (86) nicely showed that HIV, in contrast to other TLR7 agonists such as influenza virus and herpes simplex virus, induces a partially matured phenotype in pDCs. Because of this phenotype, pDCs are not rendered refractory and continue to produce type I IFNs during ongoing HIV exposure.

Interestingly, and similar to what is observed in SIV-infected SMs (102, 104) and AGMs (83), chronically HIV-infected individuals who do not progress to AIDS despite their high viral loads turned out to have very low levels of proliferating and activated T cells (117) correlating with relatively low levels of ISGs and immune activation gene expression in CD8+ T cells (118). A recent study confirmed the central role of IFNα in HIV-1 infection by showing that IFNα is the dominant type I IFN detectable in the plasma of HIV-infected individuals and that its levels correlate with immune activation and depletion of CD4+ T cells (119).

In addition, it was shown that pDCs derived from women produce...
more IFNα in response to HIV-1 than pDCs from men, resulting in higher levels of T-cell activation (120, 121). This may at least in part explain the observation that HIV-infected women with a given viral load have a 1.6-fold higher risk to develop AIDS than men, and despite having lower viral loads on average, typically progress faster to AIDS than men (122).

It has been reported that pDCs from SMs have a species-specific inability to produce high levels of type I IFN (102, 103) related to sequence polymorphisms in IRF-7, a signaling protein downstream of TLR7 and 9 (see Box 1). Also in humans, polymorphisms of IRF-7 have been reported that are associated with the level of HIV-induced IFNα production by pDCs in vitro and with CD8+ T-cell activation in vivo (123). These data stress the importance of the IRF-7 pathway in HIV pathogenesis, although there is no definite proof yet that IRF-7 itself is responsible for the induction of different responses in different individuals. Together, these observations suggest that the continuous release of type I IFNs plays a critical role in SIV and HIV pathogenesis. Future studies should point out what the direct and indirect role of IRF-7 polymorphisms is in determining the set point level of chronic immune activation in HIV-infected subjects, and should clarify the potential of IFNα and IRF-7 as drug targets (Figure 1).

**PATHOGENIC EFFECTS OF IMMUNE ACTIVATION AND INFLAMMATION**

The key role of chronic immune activation in HIV and SIV pathogenesis is now commonly accepted, as it is so clearly associated with CD4+ T-cell decline and progression to AIDS. The clinical outcome of HIV infection, however, does not only depend on CD4+ T-cell loss, but also on non-immunological side effects of chronic immune activation.

**INFLAMMATION DRIVES CD4+ T-CELL DEPLETION AND LOSS OF HIV-SPECIFIC IMMUNITY**

A large body of work has suggested that chronic immune activation in HIV infection has deleterious effects on immune function in general, as well as on HIV-specific immunity by inducing persistent activation and maturation of all sorts of innate and adaptive immune cells (82). Through continuous activation and differentiation of T cells, chronic HIV infection gradually depletes the naive CD4+ and naive CD8+ T-cell pools (31, 35, 43, 128, 129). Intrinsically different responses of the distinct T-cell lineages to activation may determine clonal expansion and contraction (130), and thereby the sensitivity of the different T-cell populations to chronic activation-induced cell loss, although the molecular basis for these differences remains unclear. Thymic and T-cell progenitor dysfunction, most likely caused by aberrantly high levels of pro-inflammatory cytokines expressed during untreated HIV infection, have been reported (43, 131) and the loss of such progenitor cells could aggravate the depleting effects of chronic immune activation on the adaptive immune system. Moreover, continuous inflammation in lymph nodes has been suggested to result in TGFβ-induced collagen deposition, fibrosis, and pathological changes in lymph node architecture, possibly adding to impaired T-cell proliferation and survival (132–134). Continuous activation has recently been shown to induce upregulation of inhibitory receptors such as programmed death-1 (PD-1), CTLA-4, and Tim-3, which may interfere with ongoing HIV-specific T-cell responses, and ultimately lead to T-cell anergy and loss of HIV-specific T cells (135–137). Similarly, B-cell dysfunction, which is observed immediately after acute HIV infection (138), is closely related to chronic activation of the B-cell compartment. Increased B-cell turnover and differentiation is associated with the phenotypic and functional B-cell abnormalities characteristic for untreated HIV infection (139–142). A recent study showed the downregulation of the regulatory receptor B- and T-lymphocyte attenuator (BTLA) and the upregulation of PD-1 on B cells in HIV infection (143). Interestingly, a direct down-regulating effect of type I IFN on BTLA expression on CD4+ and CD8+ T cells has been reported, which may directly contribute to T-cell hyperactivation (144). Recently evidence was reported for a link between PD-1L on follicular Th cells and impairment of B-cells function (145).

Persistent immune activation has also been shown to have deleterious effects on HIV-specific CD4+ (7, 146–153) and CD8+ T-cell immunity (154–160), amongst others by preventing the
establishment of IL-2-producing memory CD4+ and CD8+ T cells (146, 151–153). HIV-specific cytotoxic T-cell responses are generally considered to play an important role in anti-HIV immunity. Certain HLA alleles clearly correlate with viral load set point and disease progression. In line with this, the major genetic factors related to HIV-1 control coming out of a genome wide association study (GWAS) were shown to affect HLA–viral peptide interaction (161). There is accumulating evidence that Gag-specific CTL responses which preferentially target conserved epitopes have a protective effect (162–171). However, in two large prospective cohort studies, CD4+ and CD8+ HIV Gag-specific T-cell immunity within the first year after HIV seroconversion were not found to be predictive for disease progression (172, 173). This observation was confirmed in a longitudinal study in an African cohort (174). Also in these studies, immune activation turned out to be the strongest risk factor for disease progression, stronger than, and independent of, viral load (172, 173). It is important to consider the possibility that the typical association between strong CTL responses and a lack of HIV-disease progression that is observed in cross-sectional studies, may merely reflect the preservation of CTL responses in the absence of chronic immune activation rather than a protective effect of CTL themselves (175).

HIV-INDUCED INFLAMMATION AND HIV-ASSOCIATED NON-AIDS DISEASE

Increasing insight in the source and the role of inflammation in HIV pathogenesis has been paralleled by recent progress in our understanding of the role of inflammation in a much wider spectrum of clinical conditions than infectious diseases. After the introduction of anti-retroviral therapy for HIV infection, several case studies suggested that patients treated with cART had an increased risk to develop sub-clinical atherosclerosis and acute myocardial infarction (176–179). Initial studies reported that the increased risk of cardiovascular disease was associated with specific classes of anti-viral drugs (180). Later studies revealed that cardiovascular risk was in fact larger in untreated compared to treated HIV infection (181, 182), but also in patients on cART, the risk for cardiovascular disease is higher than expected based on traditional cardiovascular risk factors alone. In addition to cardiovascular disease, HIV infection poses patients at increased risk to develop a number of other non-AIDS related complications, such as non-alcoholic steatohepatitis, renal dysfunction, osteoporosis, insulin resistance, metabolic syndrome, and cognitive impairment (47). It has been shown that soluble mediators released by activated immune cells, such as IL-6, IL-1, and TNFα, also act on non-immune tissue cells with various tissue-dependent pathological effects. In a broad variety of clinical conditions, including obesity, atherosclerosis, neurodegenerative disease, and autoimmune diseases, chronic inflammatory processes are now recognized to play a major role (183), and it has been postulated that most non-AIDS defining complications of HIV infection are related to the chronic inflammatory state induced by HIV (Figure 1) (184, 185). This hypothesis is strengthened by recent observations in patients with rheumatoid arthritis (RA). Both HIV infection and RA are characterized by a chronic inflammatory state and increased levels of pro-inflammatory cytokines like TNFα, IL-1β, and IL-6, and also in RA patients the incidence of non-primary disease related complications such as cardiovascular disease, osteoporosis, non-alcoholic fatty liver disease (NAFLD), and cognitive impairment are more prevalent than among the general population (125–127). Thus, clinical symptoms that initially seemed unrelated are now being recognized as part of the total complex of HIV-associated disease and appear to have a common underlying pathogenesis of chronic inflammation and excessive immune activation (186, 187). Preliminary data suggest a central role for TNFα in HIV-associated non-AIDS disease but it remains to be determined to what extent other pro-inflammatory cytokines, perhaps acting via TNFα, are involved.

HIV IN COMPARISON TO OTHER PERSISTENT VIRAL INFECTIONS

These novel insights into HIV pathogenesis prompt the question as to how HIV differs from most other viruses. We believe that HIV pathogenesis is caused by a combination of specific characteristics. Most importantly HIV infects CD4+ T helper cells. In addition a variety of cells that express CD4 and one of the HIV coreceptors can be infected albeit at very low levels. Thereby, the virus is not confined to a single organ and may induce a variety of systemic immune responses. HIV induces much higher levels of cytokines during acute infection compared to hepatitis B or hepatitis C (41). HIV is virtually insensitive to control by neutralizing antibodies and cellular immunity because of various mechanisms, including the glycan shield surrounding the HIV virion (188) and the high mutation rate of the virus, which allows for rapid immune escape. After acute HIV infection, virus- and host-specific set points are established that determine the subsequent clinical course based on the level, and probably the type, of immune activation that is induced. Like other viruses, HIV induces type I IFN release by pDCs. The fact that HIV is targeted to pDCs by virtue of their expression of CD4, and the recent finding that HIV does not induce full maturation of pDC, which prevents these cells to become refractory to restimulation, as outlined above (86), may turn out to be critical factors driving persistent IFN release and thereby chronic activation of the innate and the adaptive immune system in HIV patients, resulting in exhaustion of immunity and broad spectrum end-organ immune pathology. Even though immune responses in acute hepatitis B and hepatitis C virus infection may differ from those in acute HIV infection, in individuals who do not clear hepatitis viral infection and who convert to chronic hepatitis, persistently increased immune activation levels have been reported. In analogy to what is observed in HIV patients, also non-hepatitis related conditions, such as metabolic syndrome and cardiovascular disease, occur more frequently in chronic hepatitis patients than in the general population, even when corrected for traditional risk factors for, e.g., cardiovascular disease (189). Strikingly, peripheral blood naïve T-cell numbers in chronic hepatitis C virus-infected patients were found to be significantly lower than in healthy individuals, and associated with increased levels of inflammation (190). Thus, while immune responses during acute infection may differ between HIV, hepatitis B, and hepatitis C virus infection, leading to clearance of the virus in the majority of hepatitis B infected patients and a subset of hepatitis C infected individuals, once chronic inflammation has been established, its effects tend to be similar for the three patient
groups. Other viral infections, like Epstein–Barr virus (EBV) and cytomegalovirus (CMV) are incomparable to HIV or chronic hepatitis infection, because after an acute phase these infections convert into a truly latent stage, during which no virus is detectable in the peripheral blood of immunocompetent individuals.

THE IMMUNE ACTIVATION HYPOTHESIS REDUCED TO PRACTICE

BOOSTING IMMUNITY

Great effort has been put over the years into approaches to therapeutically strengthen anti-viral immune responses. Thus far, however, there is little proof for beneficial effects, and in fact the possibility of induction of adverse effects is an important concern. Therapeutic vaccination, with DNA and live viral vector based vaccines and combinations thereof, has had only transient and small effects on viral load (191, 192). In one trial in which therapeutic vaccination was followed by interruption of cART, viral rebound was larger and time to restart therapy shorter, than in the non-vaccinated group (193). With respect to prophylactic vaccines, CTL-based vaccines may have some potential if they manage to consistently lower the viral set point. However, upon infection such vaccines will at best reduce and not completely prevent chronic immune activation driven pathogenesis and should therefore not be considered as curative. In fact, the strongest protective effect is to be expected from HIV vaccines that stimulate HLA-B57, B58, or B27 restricted T-cell responses, as they are associated with significantly lower viral loads. Such vaccines would however only help the carriers of protective HLA molecules, most of which already experience much slower disease progression upon HIV infection. In order to develop CTL vaccines that are applicable to a wider patient population it is of vital importance to gain better insight into the mechanisms responsible for the relative protection conferred by these protective HLA molecules.

For boosting of immunity and enhancement of CD4+ T-cell production, IL-2 has been administered in large scale multi-center international trials in patients with and without cART with substantial increases in CD4+ T-cell counts but no beneficial clinical effects (194). Administration of IL-7 (195, 196) or human growth hormone (197) has been tried out in small cohorts, with successful effects on naive and central memory T-cell numbers, but again without significant clinical effects. As these biological compounds are known to have strong activating effects on the peripheral T-cell compartment (198) their administration is not without risk, and one should be aware of possible adverse effects in the long run. Immune stimulating therapy should in any case be restricted to patients on cART, although even on cART (residual) immune activation is correlated with poor immune reconstitution (199). To enhance anti-HIV responses, blockade of inhibitory ligand-receptor interactions, such as PD-1, CTLA-4, and Tim-3, has been proposed (200). Some positive results have been obtained with PD-1 blockade in SIV-infected macaques, which has been shown to lead to improved virus-specific CD8+ T-cell responses, reduction in plasma viral load and prolonged survival (201), and to reduced hyperactivation and bacterial translocation (202). However, experiments with CTLA-4 blockade have demonstrated that the effects of inhibitory receptor blockade may even be deleterious, leading to increased T-cell activation and viral replication (203). Great care therefore needs to be taken with approaches that may increase the level of CD4+ T-cell proliferation, and in our opinion should never be applied without cART.

Taken together, therapeutic interventions aiming at enhancing anti-HIV T-cell immunity may not have the desired beneficial effect in the majority of people, and may even have adverse long-term effects through the immune stimulation they induce. It has been argued that since our understanding of virus-specific cellular immunity – and in particular its repertoire, its functional and kinetic requirements, and its regulation and tissue distribution – are still far from complete, the real correlate of immune protection against AIDS is still to be discovered (204). Indeed, not all immune activation needs to be equally pathogenic, and we cannot exclude the possibility that induction of HIV-specific T-cell responses without excessive and chronic release of type I IFNs and other cytokines might be favorable to the host for control of HIV. However, as pDC activation is believed to be required for the induction of an adequate adaptive T-cell response, induction of strong HIV-specific immune responses without chronic release of type I IFNs may be an impossible combination; in fact, pDC activation may collaterally cause the very same pathology that the adaptive immune response should prevent. Irrespective of the hypothesis of what is causing AIDS pathogenesis, of all vaccination strategies, prophylactic vaccines that are able to induce a strongly neutralizing antibody response at this time seem to be most promising to induce protective immunity to HIV infection in a large number of individuals (205).

THERAPEUTIC DAMAGE CONTROL

Another correlate of the immune activation hypothesis is that immune suppressive therapy might have beneficial clinical effects because it reduces the deleterious effects of immune activation. Immune suppressive drugs like cyclosporin (206, 207) and mycophenolic acid (208), that are used to prevent T-cell activation in organ transplant rejection, have been experimentally tried in HIV infection. In combination with cART, variable effects on T-cell turnover, activation, and CD4+ T-cell numbers were shown (206–208).

Given the recent insight that not activation of CD4+ and CD8+ T cells via TCR, but instead TLR activation, release of type I IFNs and expression of IFNα/β inducible genes may contribute more to systemic immune activation in HIV infection, the latter proteins and genes may be more relevant targets for therapeutic interventions (Figure 1). TLR antagonists and inhibitors are currently an area of intense investigation and it is to be expected that many will become available for phase I/II or experimental proof of concept clinical trials in the very near future (209, 210). Indeed, in a preliminary study in which chloroquine, an inhibitor of endosomal TLR3, 7, 8, and 9 was administered to HAART-naive HIV-infected patients, significantly lower immune activation levels were observed, as reflected by decreased levels of T-cell division and expression of activation markers (124). Although these findings need to be reconfirmed and more clinical studies are needed, this study suggests that interference with HIV-induced TLR7/9 activation is feasible. Because of the clear association between immune activation and clinical outcome such interventions may be promising. Also IRF-7, which selectively induces IFNα but not TNFα or
IL-12 production, is a potential drug target and treatment with IFNα neutralizing antibodies or blocking TNFα or the TNFα-R are feasible options to be explored in order to decrease inflammation and tissue-related pathology. Indeed, targeting TNFα in pathogenic SIV infection in RMs by administration of adalimumab (Humira) has been shown to reduce systemic inflammation and many of its down-stream effects (211). Humanized anti-IFNα monoclonal antibodies have been developed and have been tested in phase I trials in patients suffering from systemic lupus erythematosus (SLE) and psoriasis, autoimmune diseases in which IFNα is believed to play a critical role. In SLE but not psoriasis one dose of anti-IFNα monoclonal antibody resulted in downregulation of IFN-inducible gene expression with beneficial clinical effects (212, 213). No evidence for adverse effects, such as an increase in viral infections or viral reactivation, was observed which opens up the possibility to consider application of anti-IFNα treatment to HIV-infected patients to neutralize over-expression of IFNα. Induction of anti-IFNα antibodies by immunization with inactivated IFNα to inhibit progression to AIDS has been investigated in a large multicentre study, and beneficial effects on CD4+ T-cell decline and markers of clinical progression were reported in patients that developed anti-IFNα antibodies (214). Although these studies have never been repeated, the recently obtained insights into the role of IFNα in HIV-disease progression warrant future research in this direction. Paradoxically, IFNα administration has been investigated in the pre-cART era as a treatment option for HIV infection with or without Kaposi sarcoma (215, 216). Although IFNα treatment showed the expected anti-viral effect, leading to lower viral loads, this type of treatment became of less interest when cART became available. In addition, IFNα treatment induced flu-like syndrome, immune activation, and T-cell depletion when given to HIV patients co-infected with HCV (217–219). In RA patients who were treated with TNFα inhibiting agents (such as infliximab or etanercept) it was shown that blocking the effect of TNFα reversed the increased incidence of cardiovascular complications and insulin resistance (125–127). Anecdotal reports have shown the safety of anti-TNFα treatment in RA patients who were also HIV infected and on HAART (220). A non-specific intervention aimed at lowering immune activation and its side effects, such as cardiovascular disease, might be the addition of statins (such as infliximab or etanercept), it was shown that blocking the IFNα-R is a potential drug target and treatment with IFNα neutralizing antibodies or blocking TNFα or the TNFα-R are feasible options to be explored in order to decrease inflammation and tissue-related pathology. Indeed, targeting TNFα in pathogenic SIV infection in RMs by administration of adalimumab (Humira) has been shown to reduce systemic inflammation and many of its down-stream effects (211). Humanized anti-IFNα monoclonal antibodies have been developed and have been tested in phase I trials in patients suffering from systemic lupus erythematosus (SLE) and psoriasis, autoimmune diseases in which IFNα is believed to play a critical role. 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Immune activation and AIDS

10. Leslie AJ, Pfafferott KJ, Chetty P, Draenert R, Addo MM, Feeney M, et al. HIV evolution: CTL escape mutation and reversion after transmission. Nat Med (2004) 10(3):282–9. doi:10.1038/nm992

11. De Boer RJ, Mohri H, Ho DD, Perelson AS. Turnover rates of B cells, T cells, and NK cells in simian immunodeficiency virus-infected and uninfected rhesus macaques. J Immunol (2003) 170(5):2479–87.

12. Draenert R, Verrill CL, Tang Y, Allen TM, Wurcel AG, Boczanowski M, et al. Persistence recognition of autologous virus by high-avidity CD8+ T cells in chronic, progressive human immunodeficiency virus type 1 infection. J Virol (2004) 78(2):630–41. doi:10.1128/JVI.78.2.630-641.2004

13. Hellerstein MK, Hoh RA, Hanley MB, Cesar D, Lee D, Neese RA, et al. Subpopulations of long-lived and short-lived T cells in advanced HIV-1 infection. J Clin Invest (2003) 112(6):956–66. doi:10.1172/JCI17533

14. Grossman Z, Paul WE. The impact of HIV on naive T cell homeostasis. Nat Med (2000) 6:976–7. doi:10.1038/79667

15. Hazenberg MD, Stuart JW, Otto SA, Borlefs JC, Boucher CA, de Boer RJ, et al. T cell division in human immunodeficiency virus (HIV-1) infection is mainly due to immune activation: a longitudinal analysis in patients before and during highly active anti-retroviral therapy. Blood (2000) 95(12):2495–500.

16. Mohri H, Perelson AS, Tung K, Ribeiro RM, Ramratnam B, Fritsch P, Wachter H, et al. Markers for disease progression in HIV infection: are we closer to understanding the cause? J Infect Dis (1999) 179:859–70. doi:10.1086/314660

17. Zangerle R, Steinhuber S, Sarcletti M, Dierich MP, Wachter H, Fuchs D, et al. Serum HIV-1 RNA levels compared to soluble markers of immune activation to predict disease progression in HIV-1-infected individuals. Int Arch Allergy Immunol (1998) 116(2):228–39. doi:10.1159/000023949

18. Liu Z, Cuming WG, Hennessey K, Detels R. Elevated levels of CD38+CD8+ T cells in HIV infection add to the prognostic value of low CD4+ T cell levels; results of 6 years of follow-up. The Los Angeles Center, Multicenter AIDS Cohort Study. J Acquir Immune Defic Syndr (1993) 6:904–12.

19. Lien E, Aukrust P, Sundan A, Jansen RJ, Romadi LJ, et al. Soluble receptors for tumour necrosis factor: a putative marker of disease progression in HIV infection. AIDS (1993) 7(1):33–6. doi:10.1097/00002030-199301000-00005

20. Zangerle R, Fuchs D, Sarcletti M, Gallati H, Reibnegger G, Wachter H, et al. Reduced rate of disease development after HIV-2 infection as compared to HIV-1 infection. J Virol (2000) 74(1):209–23. doi:10.1128/JVI.74.1.209–223.2000

21. Bofill M, Mocroft A, Lipman M, Thior I, Bottiger B, Hansson LO, et al. CD4+ lymphocytes in HIV infection: relation to immune activation to predict disease progression in HIV-1-infected individuals. Multicenter AIDS Cohort Study. J Acquir Immune Defic Syndr (1998) 17(3):1881–8. doi:10.1097/00002030-200009050-00006

22. Deeks SG, Kitchen CM, Liu L, Guo H, Gascon R, Narvaez A, et al. Immune activation set point during early HIV infection predicts subsequent CD4+ T-cell changes independent of viral load. Blood (2004) 104(1):942–7. doi:10.1182/blood-2003-09-3335

23. Marlink R, Kanki P, Thior I, Travers K, Eisen G, Silvy T, et al. Reduced rate of disease development after HIV-2 infection as compared to HIV-1. Science (1994) 265:1587–90. doi:10.1126/science.8065856

24. Schramm B, Penn ML, Palacios EH, Mark GM, Kirchhof F, Goldsmith MA. Cytopathicity of human immunodeficiency virus type 2 (HIV-2) in human lymphoid tissue is coreceptor dependent and comparable to that of HIV-1. J Virol (2000) 74:9594–600. doi:10.1128/JVI.74.20.9594–600.2000

25. Grossman Z, Mierer-Schellersheim M, Sousa AE, Victorino RMM, Paul WE. CD4+ T-cell depletion in HIV infection: are we closer to understanding the cause? Nat Med (2002) 8:319–23. doi:10.1038/nm4002-319

26. Sousa AE, Carneiro J, Mierer-Schellersheim M, Grossman Z, Victorino RM. CD4+ T cell depletion is linked directly to immune activation in the pathogenesis of HIV-1 and HIV-2 but only indirectly to the viral load. J Immunol (2002) 169(6):3400–6.

27. Chakrabarti LA, Lewin SR, Zhang L, Gettie A, Luckay A, Martin LN, et al. Normal T cell turnover in sooty mangabeys harboring active simian immunodeficiency virus infection. J Virol (2000) 74(1):209–23. doi:10.1128/JVI.74.1.209–223.2000

28. Silvestri G, Sodora DL, Koup RA, Paiardini M, O’Neil SP, Mc Craile HM, et al. Nonpathogenic SIV infection of sooty mangabeys is characterized by limited bystander immunopathology despite chronic high-level viremia. Immunity (2003) 18(3):441–52. doi:10.1016/S1074-7613(03)00060-8

29. Hazenberg MD, Hamann D, Schuetzler H, Miedema F. T cell depletion in HIV-1 infection: how CD4+ T cells go out of stock. Nat Immunol (2000) 1(4):285–9. doi:10.1038/79724

30. Pedersen C, Lindhardt BO, Jensen BL, Lauritzen E, Gerstoft J, Dickmeiss E, et al. Clinical course of primary HIV infection: consequences for subsequent course of infection. BMJ (1989) 299(6692):699–702. doi:10.1136/bmj.299.6692.154

31. Stacey AR, Norris PJ, Qin L, Hay- green EA, Taylor E, Heitman I, et al. Induction of a striking systemic cytokine cascade prior to peak viremia in acute human immunodeficiency virus type 1 infection, in contrast to more modest and delayed responses in acute hepatitis B and C viruses and in HIV. J Virol (2009) 83(8):3719–33. doi:10.1128/JVI.01844-08

32. Girardi E, Mocroft A, Lewin SR, von Steuding LV, Biberfeld G, Bottiger B, Hansson LO, et al. Immunological changes in primary HIV-1 infection. AIDS (1999) 13(10):995–9. doi:10.1097/00002030-199910000-00008

Miedema et al.
43. Douek DC, Picker LJ, Koup RA. T cell dynamics in HIV-1 infection. Annu Rev Immunol 2003;21:265–304. doi:10.1146/annurev.immunol.21.120600.114053
44. Clark DR, De Boer RJ, Wolthers KC, Miedema F. T cell dynamics in HIV-1 infection. Adv Immunol 1999;73:301–27. doi:10.1016/S0065-2778(03)67890-9
45. Elbim C, Pellet S, Prevost MH, Preira A, Girard PM, Rogine N, et al. Redox and activation status of monocytes from human immunodeficiency virus-infected patients: relationship with viral load. J Virol 1999;73(6):4561–6.
46. Elbim C, Prevost MH, Boucarat F, Franzini E, Chollet-Martin S, Hakim J, et al. Polymorphonuclear neutrophils from human immunodeficiency virus-infected patients show enhanced activation, diminished iNLP-induced L-selectin shedding, and an impaired oxidative burst after cytokine priming. Blood 1998;92(10):2759–66.
47. Deeks SG. HIV infection, inflammation, immunosenescence, and aging. Annu Rev Med 2011;62:141–55. doi:10.1146/annurev.med-042909-093756
48. Venez YR, DeMaria M, Chali-foux LV, Shvetz DE, Pauley DR, Knight HL, et al. Gastrointestinal tract as a major site of CD4+ T cell depletion and viral replication in SIV infection. Science 1998;280(5362):427–31. doi:10.1126/science.280.5362.427
49. Brenchley JM, Schacker TW, Ruff LE, Price DA, Taylor JH, Beilman GJ, et al. CD4+ T cell depletion during all stages of HIV disease occurs predominantly in the gastrointestinal tract. J Exp Med 2004;200(6):749–59. doi:10.1084/jem.20040874
50. Li Q, Duan L, Estes JD, Ma ZM, Bourque T, Wang Y, et al. Peak SIV replication in resting memory CD4+ T cells depletes gut lamina propria CD4+ T cells. Nature (2005) 434(7037):1148–52.
51. Brenchley JM, Price DA, Schacker TW, Asher TE, Silvestri G, Rao S, et al. Microbial translocation is a cause of systemic immune activation in chronic HIV infection. Nat Med 2006;12(12):1365–71. doi:10.1038/nm1511
52. Gordon SN, Asher TE, Odorizzi P, Silverman R, Albera F, Ginsberg G, et al. Disruption of intestinal CD4+ T cell homeostasis is a key marker of systemic CD4+ T cell activation in HIV-infected individuals. J Immunol (2010) 185(9):5169–79. doi:10.4049/jimmunol.1001801
53. Brenchley JM, Price DA, Douek DC. HIV disease: fallout from a mucosal catastrophe? Nat Immunol 2006;7(3):235–9. doi:10.1038/ni1316
54. Gordon SN, Klatt NR, Bosinger ME, Price DA, Taylor JH, Beilman GJ, et al. CD4+ T cell activation in HIV-infected South Africans receiving combination antiretroviral therapy. J Infect Dis 2010;202(5):723–33. doi:10.1086/655229
55. Wallace MA, Rodrigues CA, Yin L, Saporta S, Chirmatragi A, Ho W, et al. Microbial translocation induces persistent macrophage activation unrelated to HIV-1 levels or T cell activation following therapy. AIDS (2010) 24(9):1281–90. doi:10.1097/QAD.0b013e3283e228
56. Pandev IA, Gautam R, Ribeiro RM, Brenchley JM, Butler IF, Patterson T, et al. Acute loss of intestinal CD4+ T cells is not predictive of simian immunodeficiency virus virulence. J Immunol (2007) 179(5):3035–46.
57. Breed MJ, Jordan AP, Aye PP, Lichtveld CF, Midkiff CC, Schiro FR, et al. Loss of tyrosine-dependent trafficking motif in the simian immunodeficiency virus envelope cytoplasmic tail spares mucosal CD4 cells but does not prevent disease progression. J Virol (2013) 87(13):5128–43. doi:10.1128/JVI.01928-12.
58. Marchetti G, Bellistri GM, Borghi E, Tincati G, Ferramossa S, La FM, et al. Microbial translocation is associated with sustained failure in CD4+ T-cell reconstitution in HIV-infected patients on long-term highly active antiretroviral therapy. AIDS (2008) 22(15):2035–8. doi:10.1097/QAD.0b013e32812d229
59. Deeks SG, Phillips AN. HIV infection, antiretroviral treatment, aging, and non-AIDS related morbidity. BMJ (2009) 338:a3172. doi:10.1136/bmj.a3172
60. Kalayan-Raj GC, Machakeno RN, Rzmk N, Robbins GK, Gandhi RT, Rodriguez BA, et al. Pretreatment levels of soluble cellular receptors and interleukin-6 are associated with HIV disease progression in subjects treated with highly active antiretroviral therapy. J Infect Dis (2010) 201(12):1796–805. doi:10.1086/652750
61. Jiang W, Lederman MM, Hunt P, Sieg SF, Haley K, Rodriguez B, et al. Plasma levels of bacterial DNA correlate with immune activation and the magnitude of immune restoration in persons with antiretroviral-treated HIV infection. J Infect Dis (2009) 199(8):1177–85. doi:10.1086/597476
62. Cassel E, Malféld S, Mahasha P, van der Merwe MS, Cassol S, Seebregts C, et al. Persistent microbrial translocation and immune activation in HIV-1-infected South Africans receiving combination antiretroviral therapy. J Infect Dis (2010) 202(5):723–33. doi:10.1086/655229
63. Baroncelli S, Galluzzo CM, Pirillo MF, Mancini MG, Weiner LE, Andreotti M, et al. Microbial translocation is associated with residual viral replication in HAART-treated HIV+ subjects with <50copies/ml HIV-1 RNA. J Clin Virol (2009) 46(4):367–70. doi:10.1016/j.jcv.2009.09.011
64. Brenchley JM, Piardini M, Knox KS, Asher A, Cervasi B, Asher TE, et al. Differential Th17 CD4+ T-cell depletion in pathogenic and non-pathogenic lentiviral infections. Blood (2008) 112(7):2826–35. doi:10.1182/blood-2008-05-15928.
65. Littman DR, Rudensky AY. Th17 and regulatory T cells in mediating and restraining inflammation. Cell (2010) 140(6):845–58. doi:10.1016/j.cell.2010.02.021
66. Favre D, Lederer S, Kanwar B, Ma ZM, Proll S, Kasakow Z, et al. Critical loss of the balance between Th17 and T regulatory cell populations in pathogenic SIV infection. PLoS Pathog (2009) 5(2):e1000295. doi:10.1371/journal.ppat.1000295
67. Raffatellu M, Santos RL, Verhoeven DE, George MD, Wilson RP, Winter SE, et al. Simian immunodeficiency virus-induced mucosal interleukin-17 deficiency promotes Salmonella dissemination from the gut. Nat Med (2008) 14(4):421–8. doi:10.1038/nm1743
68. Mici L, Cervasi B, Ende ZS, Iriei RE, Reyes-Aviles E, Vinton C, et al. Paucity of IL-21-producing CD4+ T cells is associated with HIV disease progression in human immunodeficiency virus type 1–encoded toll-like receptor ligands. J Virol (2007) 81(15):8180–91. doi:10.1128/JVI.01421-07.
69. Fonteneau JJ, Larsson M, Beignon AS, McKenna K, DaSilva I, Amara A, et al. Human immunodeficiency virus type 1 activates plasmacytoid dendritic cells and concomitantly induces the bystander maturation of myeloid dendritic cells. J Virol (2004) 78(10):5223–32. doi:10.1128/JVI.78.10.5223-5232.2004
70. Hardy AW, Graham DR, Shearer GM, Herbeuvel JP. HIV turns plasmacytoid dendritic cells (pDC) into TRAIL-expressing killer pDC and down-regulates HIV coreceptor binding by toll-like receptor 7–induced IFN-alpha. Proc Natl Acad Sci U S A (2007) 104(14):5745–8. doi:10.1073/pnas.0707244104.
71. Alter G, Suscovich TJ, Teigen N, Meier A, Streeck H, Brandt C, et al. Single-stranded RNA derived from HIV-1 serves as a potent activator of NK cells. J Immunol (2007) 178(12):7658–66.
72. Sedaghat AR, German J, Telovolich TM, Cofrancesco J Jr, Ie CC, Talbot CC Jr, et al. Chronic CD4+ T cell activation and depletion in human immunodeficiency virus type 1 interferon-mediated disruption of T cell dynamics. J Virol (2008) 82(4):1870–83. doi:10.1128/JVI.02228-07.
73. Hyrcza MD, Kovacs C, Loutfy M, Heisler L, Yang S, et al. Effect of antiviral therapy on mucosal inflammatory markers in HIV-infected individuals. J Infect Dis (2012) 206:1601–11. doi:10.1093/infdis/jir413.
et al. Distinct transcriptional profiles in ex vivo CD4+ and CD8+ T cells are established early in human immunodeficiency virus type 1 infection and are characterized by a chronic interferon response as well as extensive transcriptional changes in CD8+ T cells. J Virol (2007) 81(7):3477–86. doi:10.1128/JVI.01552-06

79. Cohen Stuart JW, Hazenberg MD, Hamann D, Otto SA, Borleffs JC, Miedema F, et al. The dominant source of CD4+ and CD8+ T-cell activation in HIV infection is antigenic stimulation. J Acquir Immune Defic Syndr (2000) 25(3):203–11. doi:10.1097/00126334-200011010-00001

80. Bucy RP, Hockett RD, Derdeyn CA, Saag MS, Squires K, Sillers M, et al. Initial increase in blood CD4+ lymphocytes after HIV anti-retroviral therapy reflects redistribution from lymphoid tissues. J Clin Invest (1999) 103(10):1391–8. doi:10.1172/JCI97586

81. Wolf K, Tsakiris DA, Weber R, Erb P, Battegay M. Antiretroviral therapy reduces markers of endothelial and coagulation activation in patients infected with human immunodeficiency virus type 1. J Infect Dis (2002) 185(4):456–62. doi:10.1086/338572

82. Theofilopoulos AN, Baccala R, Beutler B, Kono DH. Type I interferons (alpha/beta) in immunity and autoimmune disease. Annu Rev Immunol (2005) 23:307–36. doi:10.1146/annurev.immunol.23.012004.071543

83. Jacqueline B, Mayau V, Tarbet B, Liovat AS, Kunkel D, Petitjean G, et al. Nonpathogenic SIV infection of African green monkeys induces a strong but rapidly controlled type I IFN response. J Clin Invest (2009) 119(12):3512–5. doi:10.1172/JCI41505

84. Manches O, Bhardwaj N. Resolving the enigma of the AIDS paradox. J Immunol (2007) 179(5):3047–56.

85. Barry AP, Silvestri G, Safrit JT, Sumpter B, Kozyr N, McClure HM, et al. Depletion of CD8+ cells in sooty mangabey monkeys naturally infected with simian immunodeficiency virus reveals limited role for immune control of virus replication in a natural host species. J Immunol (2007) 178(12):8002–12.

86. Gordon SN, Dunham RM, Engram JC, Estes I, Wang Z, Klatt NR, et al. Short-lived infected cells support virus replication in sooty mangabeyes naturally infected with simian immunodeficiency virus: implications for AIDS pathogenesis. J Virol (2008) 82(7):3725–35. doi:10.1128/JVI.02408-07

87. Kornfeld C, Ploquin MJ, Pandrea I, Faye A, Onanga R, Apetrei C, et al. Antinflammatory profiles during primary SIV infection of sooty mangabees is independent of cellular immunity to the virus. Blood (2006) 107(6):2423–31. doi:10.1182/blood-2005-07-2709

88. Meythaler M, Martinet A, Wang Z, Przytupiewicz S, Keshava M, Ling B, et al. Differential CD4+ T-lymphocyte apoptosis and bystander T-cell activation in rhesus macaques and sooty mangabees during acute simian immunodeficiency virus infection. J Virol (2009) 83(2):572–83. doi:10.1128/JVI.01715-08

89. Mandl JN, Akondy R, Lawson B, Kozyr N, Staprans SI, Ahmed R, et al. Distinctive TLR7 signaling, type I IFN production, and attenuated innate and adaptive immune responses to yellow fever virus in a primate reservoir host. J Immunol (2011) 186(11):6406–16. doi:10.4049/jimmunol.1001191

90. Boztug SE, Li Q, Gordon SN, Klatt NR, Duan L, Xu L, et al. Global genomic analysis reveals rapid control of a robust innate response in SIV-infected sooty mangabees. J Clin Invest (2009) 119(12):3556–72. doi:10.1172/JCI40115

91. Harris LD, Tabb B, Sodora DL, Piaiardin M, Klatt NR, Douek DC, et al. Down-regulation of robust acute type I IFN responses distinguishes non-pathogenic SIV infection of natural hosts from pathogenic SIV infection of rhesus macaques. J Virol (2010) 84(15):7886–91. doi:10.1128/JVI.02612-09

92. Lederer S, Favre D, Walters KA, Proll S, Kanzbar B, Kaszkow Z, et al. Transcriptional profiling in pathogenic and non-pathogenic SIV infections reveals significant distinctions in kinetics and tissue compartmentalization. PLoS Pathog (2009) 5(2):e1000296. doi:10.1371/journal.ppat.1000296

93. Joshi RD, Gordon SN, Zeng M, Chahrroudi AM, Dunham RM, Staprans SI, et al. Early resolution of acute immune activation and induction of PD-1+ in SIV-infected sooty mangabees distinguishes nonpathogenic from pathogenic infection in rhesus macaques. J Immunol (2008) 180(10):6789–807.

94. Meythaler M, Martinet A, Wang Z, Przytupiewicz S, Keshava M, Ling B, et al. Differential CD4+ T-lymphocyte apoptosis and bystander T-cell activation in rhesus macaques and sooty mangabees during acute simian immunodeficiency virus infection. J Virol (2008) 82(3):572–83. doi:10.1128/JVI.01715-08

95. Mandl JN, Akondy R, Lawson B, Kozyr N, Staprans SI, Ahmed R, et al. Distinctive TLR7 signaling, type I IFN production, and attenuated innate and adaptive immune responses to yellow fever virus in a primate reservoir host. J Immunol (2011) 186(11):6406–16. doi:10.4049/jimmunol.1001191

96. Boztug SE, Li Q, Gordon SN, Klatt NR, Duan L, Xu L, et al. Global genomic analysis reveals rapid control of a robust innate response in SIV-infected sooty mangabees. J Clin Invest (2009) 119(12):3556–72. doi:10.1172/JCI40115

97. Harris LD, Tabb B, Sodora DL, Piaiardin M, Klatt NR, Douek DC, et al. Down-regulation of robust acute type I IFN responses distinguishes non-pathogenic SIV infection of natural hosts from pathogenic SIV infection of rhesus macaques. J Virol (2010) 84(15):7886–91. doi:10.1128/JVI.02612-09

98. Lederer S, Favre D, Walters KA, Proll S, Kanzbar B, Kaszkow Z, et al. Transcriptional profiling in pathogenic and non-pathogenic SIV infections reveals significant distinctions in kinetics and tissue compartmentalization. PLoS Pathog (2009) 5(2):e1000296. doi:10.1371/journal.ppat.1000296

99. Joshi RD, Gordon SN, Zeng M, Chahrroudi AM, Dunham RM, Staprans SI, et al. Early resolution of acute immune activation and induction of PD-1+ in SIV-infected sooty mangabees distinguishes nonpathogenic from pathogenic infection in rhesus macaques. J Immunol (2008) 180(10):6789–807.

100. Meythaler M, Martinet A, Wang Z, Przytupiewicz S, Keshava M, Ling B, et al. Differential CD4+ T-lymphocyte apoptosis and bystander T-cell activation in rhesus macaques and sooty mangabees during acute simian immunodeficiency virus infection. J Virol (2008) 82(3):572–83. doi:10.1128/JVI.01715-08

101. Mandl JN, Akondy R, Lawson B, Kozyr N, Staprans SI, Ahmed R, et al. Distinctive TLR7 signaling, type I IFN production, and attenuated innate and adaptive immune responses to yellow fever virus in a primate reservoir host. J Immunol (2011) 186(11):6406–16. doi:10.4049/jimmunol.1001191

102. Boztug SE, Li Q, Gordon SN, Klatt NR, Duan L, Xu L, et al. Global genomic analysis reveals rapid control of a robust innate response in SIV-infected sooty mangabees. J Clin Invest (2009) 119(12):3556–72. doi:10.1172/JCI40115

103. Mandl JN, Akondy R, Lawson B, Kozyr N, Staprans SI, Ahmed R, et al. Distinctive TLR7 signaling, type I IFN production, and attenuated innate and adaptive immune responses to yellow fever virus in a primate reservoir host. J Immunol (2011) 186(11):6406–16. doi:10.4049/jimmunol.1001191
lentivirus infections. *Immunity* (2010) 32(6):677–84. doi:10.1016/j.immuni.2010.06.004

111. Estes JD, Harris LD, Klatt NR, Tabb B, Piltulla S, Paidirini M, et al. Damaged intestinal epithelial integrity linked to microbial translocation in pathogenic simian immunodeficiency virus infections. *PLoS Pathog* (2010) 6(6): e1001052. doi:10.1371/journal.ppat.1001052

112. Paidirini M, Cervasti B, Reyes-Aviles E, Maci L, Ortiz AM, Chahroudi A, et al. Low levels of SIV infection in sooty mangabeys central memory CD4+ T cells are associated with limited CCR5 expression. *Nat Med* (2011) 17(7):830–6. doi:10.1038/nm.2395

113. Beaumier CM, Harris LD, Goldsmith E, Miedema F, et al. Low immune dysregulation by memory CD4+ T cells in vivo renders African green monkeys resistant to progressive SIVagm infection. *J Clin Invest* (2009) 119(8):2242–9. doi:10.1172/JCI39257

114. Ganesan A, Chattopadhyay PK, McGinty J, et al. CD4 down-regulation with limited CCR5 expression. *CD4(+) T cells are associated with the acquired immunodeficiency syndrome.* *N Engl J Med* (2001) 344(10):720–5. doi:10.1056/NEJM200103083441003

115. Schneider DS, Ayres JS. Two ways to survive infection: what resistance and tolerance can teach us about treating infectious diseases. *Rev Immunol* (2008) 7(1):109–15. doi:10.1016/j.revim.2007.11.012

116. Medzhitov R. Damage control in host-pathogen interactions. *Proc Natl Acad Sci U S A* (2009) 106(57):25552–6. doi:10.1073/pnas.0908451106

117. Choudhary SK, Vrisekoop N, Jansen CA, Otto SA, Schuitemaker H, Miedema F, et al. Low immune activation despite high levels of pathogenic human immunodeficiency virus type 1 results in long-term asymptomatic disease. *J Virol* (2007) 81(16):8838–42. doi:10.1128/JVI.02663-06

118. Rotger M, Dalmun J, Rauch A, McLaren P, Bosinger SE, Martinez M, et al. Comparative transcriptomics of extreme phenotypes of human HIV-1 infection and SIV infection in sooty mangabeys and rhesus macaque. *J Clin Invest* (2011) 121(6):2391–400. doi:10.1172/JCI45235

119. Hardy GA, Sieg S, Rodriguez B, Anthony D, Asaad R, Jiang W, et al. Interferon-alpha in the primary plasma type-1 IFN in HIV-1 infection and correlates with immune activation and disease markers. *PLoS One* (2013) 8(2): e5627. doi:10.1371/journal.pone.0056527

120. Meier A, Chang HJ, Chan ES, Pollard RB, Sidhu HK, Kulkarni S, et al. Sex differences in the toll-like receptor-mediated response of plasmacytoid dendritic cells to HIV-1. *Nat Med* (2009) 15(8):955–9. doi:10.1038/nm.2004

121. Chang JJ, Woods M, Lindsay RJ, Doyle EH, Griesbeck M, Chan ES, et al. Higher expression of several interferon-stimulated genes in HIV-1 infected females after adjusting for the level of viral replication. *J Infect Dis* (2013) 206(5):830–8. doi:10.1093/infdis/jit262

122. Sterling TR, Vladov D, Astemborski J, Hoover DR, Margolick JB, Quinn TC. Initial plasma HIV-1 RNA levels and progression to AIDS in women and men. *N Engl J Med* (2001) 344(10):720–5. doi:10.1056/NEJM200103083441003

123. Chang J, Lindsay RJ, Kulkarni S, Lifson JD, Carrington M, Altman D, et al. Longitudinal study of immune function in patients on inflammatory mechanisms. *Sci Adv* (2018) 4(1):330–43. doi:10.1126/sciadv.aau7677

124. Murray SM, Down CM, Boulware DR, Stauffer WM, Cavert WP, et al. Higher expression of several CCR5-related genes correlates with limited CCR5 expression. *CD4+ but not CD8+ T cells in vivo render CD4+ memory T cells in rapidly progressive simian immunodeficiency virus infection. J Exp Med* (2004) 200(10):1299–314. doi:10.1083/jem.20041049

125. Inderbitzin EF, Daly LM, Sylvestri G, et al. B-lymphocyte activation and T cell depletion in HIV-1 infection. *J Clin Invest* (2002) 110(8):1133–9. doi:10.1172/JCI200216413

126. Schacker TW, Nguyen PL, Beilke PJ, Miranda-Filloy JA, Llorca J, Juanatey C, et al. Higher expression of several polymorphisms in interferon regulatory factor 7 reduce T-cell progenitor function during progressive human immunodeficiency virus-1 infection and after antiretroviral therapy. *Blood* (2000) 96(1):242–9.

127. Schacker TW, Nguyen PL, Beilman GJ, Wolinsky S, Larson, Reilly C, et al. Collagen deposition in HIV-1 infected lymphatic tissues and T cell homeostasis. *J Clin Invest* (2002) 110(8):1133–9. doi:10.1172/JCI200216413

128. Roederer M, Gregson Dubs J, Inderbitzin EF, Daly LM, Sylvestri G, et al. T-cell progenitor function during progressive human immunodeficiency virus-1 infection and after antiretroviral therapy. *Blood* (2000) 96(1):242–9.

129. Schacker TW, Nguyen PL, Beilman GJ, Wolinsky S, Larson, Reilly C, et al. Collagen deposition in HIV-1 infected lymphatic tissues and T cell homeostasis. *J Clin Invest* (2002) 110(8):1133–9. doi:10.1172/JCI200216413

130. Martinez-Maza O, Crabb E, Mit-suyasu RT, Fahey JL, Giorgi JV. Infection with the human immunodeficiency virus (HIV) is associated with in vivo increase in B lymphocyte activation and immuno- tropy. *J Immunol* (1987) 138:3720–4.

131. Caggiati A,Nilsson A, De Milito A, Chiiodi F. B cell immunopathology during HIV-1 infection: lessons to learn for HIV-1 vaccine design. *Vaccine* (2008) 26(42):5016–25. doi:10.1016/j.vaccine.2007.11.063

132. Moreland LW, Curtis JR. Systemic nonarticular manifestations of rheumatoid arthritis: focus on the impact of the anti-TNF-alpha pathway. *Ann N Y Acad Sci* (2010) 1193:153–9. doi:10.1111/j.1749-6646.2009.05287.x

133. Estes JD, Wietgrefe S, Schacker T, Southern P, Beilman G, Reilly C, et al. Simian immunodeficiency virus-induced lymphatic tissue fibrosis is mediated by transforming growth factor beta 1-positive regulatory T cells and begins in early infection. *J Infect Dis* (2007) 195(4):551–61. doi:10.1086/510852

134. Zeng M, Smith AJ, Wietgrefe SW, Southern P, Schacker TW, Reilly CS, et al. Cumulative mechanisms of lymphoid tissue fibrosis and T cell depletion in HIV-1 and SIV infections. *J Clin Invest* (2011) 121(3):998–1008. doi:10.1172/JCI45157

135. Day CL, Kaufmann DE, Kiepiela P, Brown JA, Moodley ES, Reddy S, et al. PD-1 expression on HIV-specific T cell is associated with T-cell exhaustion and disease progression. *Nature* (2006) 443(7109):350–4. doi:10.1038/nature05115

136. Trautmann L, Janbazian L, Chomont N, Said EA, Gimmi S, Bessette B, et al. Upregulation of PD-1 expression on HIV-specific CD4+ T cells leads to reversible immune dysfunction. *Nat Med* (2006) 12(10):1198–202. doi:10.1038/nm1329b

137. Kaufmann DE, Kavanagh DH, Pereyra F, Zaunders J, Mackey EW, Mora T, et al. Upregulation of CTLA-4 by HIV-specific CD4+ T cells correlates with disease progression and defines a reversible immune dysfunction. *Nat Immunol* (2007) 8(11):1246–54. doi:10.1038/nm1515

138. Terpstra FG, Al BJ, Roos MT, De Wolf F, Goudsmitt J, Schellekens PT, et al. Longitudinal study of leukocyte functions in homosexual men seroconverted for HIV-1: rapid and persistent loss of B cell function after HIV-1 infection. *Eur J Immunol* (1989) 19:667–73. doi:10.1002/eji.1830190415

139. Lane HC, Depper JL, Greene WC, Whalen G, Waldmann TA, Fauci AS. Qualitative analysis of immune function in patients with the acquired immunodeficiency syndrome. *N Engl J Med* (1985) 313:79–84. doi:10.1056/NEJM1985113012004

140. Martinez-Maza O, Crabb E, Mitsu-suyasu RT, Fahey JL, Giorgi JV. Infection with the human immunodeficiency virus (HIV) is associated with in vivo increase in B lymphocyte activation and immuno- tropy. *J Immunol* (1987) 138:3720–4.
Metcalf T, et al. Inadequate T follicular cell help impairs B cell immunity during HIV infection. Nat Med (2013) 19(4):494–9. doi:10.1038/nm.3109

146. Younes SA, Yassine-Diab B, Dumont AR, Boullasser ML, Grossman Z, Routu JP, et al. HIV-1 viremia prevents the establishment of interleukin 2-producing HIV-specific memory CD4+ T cells endowed with proliferative capacity. J Exp Med (2003) 198(12):2099–20. doi:10.1084/jem.20031598

147. McNeil AC, Shupert WL, Iyasere CA, Hallahan CW, Mcan JA, Davey RT Jr, et al. High-level HIV-1 viremia suppresses viral antigen-specific CD4+ T cell proliferation. Proc Natl Acad Sci U S A (2001) 98(24):13878–83. doi:10.1073/pnas.25135998

148. Kaufman D, Lichterfeld M, Alt- feld M, Allen TM, Johnston M, Lee P, et al. Limited durability of immune control following treated acute HIV infection. PLoS Med (2004) 1(2):e36. doi:10.1371/ journal.pmed.0010036

149. Jansen CA, De Cuyper IM, Ste- ingrover R, Jarrahi S, Sankatsi- ing SUC, Prins JM, et al. Analysis of the effect of highly active antiretroviral therapy during acute HIV-1 infection on HIV-specific CD4+ T-cell functions. AIDS (2005) 19(14):54–5. doi:10.1097/01.aids.0000180468.82781.2b

150. Jansen CA, Piriou E, De Cuyper IM, van Dort K, Lange JM, Miedema F, et al. Long-term highly active antiretroviral therapy in chronic HIV-1 infection: evidence for reconstitution of antivi- ral immunity. Antivir Ther (2006) 11(1):105–16.

151. Harari A, Petitpierre S, Valkelian F, Pantaleo G. Skewed representation of functionally distinct pop-ulations of virus-specific CD4 T cells in HIV-infected subjects with progressive disease: changes after antiretroviral ther-apy. Blood (2004) 103(3):906–72. doi:10.1182/blood-2003-04-1203

152. Harari A, Valkelian F, Pantaleo G. Phenotypic heterogeneity of antigen-specific CD4 T cells under different conditions of antigen per- sistence and antigen load. Eur J Immunol (2005) 35(1):252–3. doi:10.1002/eji.200425324

153. Harari A, Valkelian F, Meylan PR, Pantaleo G. Functional het- erogeneity of memory CD4 T cell responses in memory condi- tions of antigen exposure and persistence. J Immunol (2005) 174(2):1037–45.

154. Migueles SA, Laborico AC, Shu- pert WL, Sabaghian MS, Rabin R, Hallahan CW, et al. HIV- specific CD8+ T cell proliferation is coupled to perforin expression and is maintained in non-progressors. Nat Immunol (2002) 3(11):1061–8. doi:10.1038/nri8485

155. Chapman P, Ogg GS, King AS, Knobenhans C, Ellefsen K, Nobile M, et al. Skewed maturation of memory HIV- specific CD8 T lymphocytes. Nature (2001) 410:106–11. doi:10.1038/35065118

156. Betts MR, Krowka JF, Kepler TB, Davidian M, Christopherson C, Kwock S, et al. Human immunodefi-cency virus type 1-specific cytotoxic T lymphocyte activity is inversely correlated with HIV type 1 viral load in HIV type 1-infected long-term sur- vivors. AIDS Res Hum Retroviruses (1999) 15(13):1219–28. doi:10.1089/0898922993105313

157. Betts MR, Ambrozak DR, Douek DC, Bonhoeffer S, Brenchley JM, Casazza JP, et al. Analysis of total human CD8+ T-cell responses: rapid ageing dur- ing chronic stimulation of the CD8+ T cells in HIV-1-infected sub- type C infection. J Virol (2003) 77(24):11983–91. doi:10.1128/JVI. 75.24.11983-11991.2001

158. Appay V, Dunbar PR, Callan M, Knelsen P, Gillespie GM, Papagno L, et al. Memory CD8+ T lymphocytes and viral replica-tion in human immunodeficiency virus-infected children. J Infect Dis (2002) 186(11):1589–96. doi:10.1086/364582

159. van Baarle D, Tsegaye A, Miedema F, et al. Abundance and linkage of HIV evolution reveals regions of immunological vulner- ability. Proc Natl Acad Sci U S A (2011) 108(28):11530–5. doi:10.1073/pnas.110531508

160. Goepfert PA, Lumen W, Farmer P, Mathews P, Prendergast A, Carl- son JM, et al. Transmission of HIV-1 Gag immune escape muta-tions is associated with reduced viral load in linked recipients. J Exp Med (2008) 205(5):1809–17. doi:10.1084/jem.20072457

161. Schellens IM, Borghans J, Jansen CA, De Cuyper IM, Geskus RB, van Baarle D, et al. Abundance of early functional HIV-specific CD8+ T cells does not predict AIDS-free survival time. PLoS One (2008) 3(7):e2745. doi:10.1371/ journal.pone.0002745

162. Jansen CA, De Cuyper IM, Hosnib- rink B, van der Bij AK, van Baarle D, Miedema F. Prognos- tic value of HIV-1 Gag-specific CD4+ T-cell responses for pro-gression to AIDS analysed in a prospective cohort study. Blood (2004) 103(7):1427–33. doi:10.1182/blood-2003-05-2097

163. Brumme Z, Wang B, Nair K, Brumme C, de Pierreis C, Reddy S, et al. Impact of select immunono- logic and virologic biomarkers on CD4 cell count decrease in patients with chronic HIV-1 sub- type C infection: results from Sinikhemba Cohort, Durban, South Africa. Clin Infect Dis (2009) 49(6):956–64. doi:10.1086/605503

164. Jansen CA, van Baarle D, Miedema F. HIV-specific CD4+ T cells and viremia: who’s in control? Trends Immunol (2006) 27(3):119–24. doi:10.1016/j.tiim.2006.01.004

165. Henry K, Melroe H, Huibsch J, Hermundson J, Levine C, Swensen L, et al. Severe pre-mature coronary artery disease with protease inhibitors. Lancet (1998) 351(9128):1322. doi:10.1016/S0140-6736(97)80505-X

166. Gibbs MJ, Mannon MR, Williamson JM, Tong TC, Ward DJ, Wood KC, et al. Protease inhibitors and cardiovascular outcomes in patients with HIV-1. Lancet (2002) 360(9347):1747–8. doi:10.1016/S0140-6736(02)11672-2

167. Mary-Krause M, Cotte L, Simon A, Parissian S, Costagliola D. Increased risk of myocardial infarction with duration of protease inhibitor therapy in...
185. Hsue PY, Hunt PW, Schnell A, Hsue PY, Hunt PW, Sinclair E, et al. Immune activation and AIDS. J Exp Med (2008) 205(7):1701–14. doi:10.1084/jem.20071681
186. Napolitano LA, Schmidt DJ, Gotowiec MB, Ameli N, Fibelt EL, Ng MM, et al. Growth hormone enhances thymic function in HIV-1-infected adults. J Clin Invest (2008) 118(3):1085–98.
187. Sereti I, Dunham RM, Spritzler J, Aga E, Proschan MA, Medvik K, et al. IL-7 administration drives T cell-cycle entry and expansion in HIV-1 infection. Blood (2009) 113(23):6304–14. doi:10.1182/blood-2008-10-168601
188. Deeks SG, Barbour JD, Grant RM, Martin JN. Duration and predictors of CD4 T-cell gains in patients who continue combination therapy despite detectable plasma viremia. AIDS (2002) 16(2):201–7. doi:10.1097/00002030-200202150-00009
189. Kaufmann DE, Walker BD. PD-1 and CTLA-4 inhibitory coinigaling pathways in HIV infection and the potential for therapeutic intervention. J Immunol (2009) 182(10):5891–7. doi:10.4443/jimmunol.0803771
190. Velu V, Titanji K, Zhu B, Husain S, Pladevégia A, Lai L, et al. Enhancing SIV-specific immunity in vivo by PD-1 blockade. Nature (2009) 458(7235):206–10. doi:10.1038/nature07662
191. Dayrav SR, Velu V, Titanji K, Bosinger SE, Freeman GJ, Silvestri G, et al. PD-1 blockade during chronic SIV infection reduces hyperimmune activation and microbial translocation in rhesus macaques. J Clin Invest (2012) 122(5):1712–6. doi:10.1172/JCI66012
192. Cecchinato V, Tryniszewska E, Ma HN, et al. A randomized, double-blind, placebo-controlled, phase I study of MEDI-545, an anti-tumor necrosis factor antibody, in subjects with chronic psoriasis. J Am Acad Dermatol (2010) 62(3):427–36. doi:10.1016/j.jaad.2009.05.042
193. Papp R, Goerz G, van der Meer SC, Gonda J, Ruzicka T, et al. Enhancement of T cell recovery in HIV-infected adults through IL-7 treatment. J Clin Invest (2012) 122(5):1712–6. doi:10.1172/JCI66012
194. Virgin HW, Walker BD. Immunology and the elusive AIDS vaccine. Nature (2010) 464(7286):224–31. doi:10.1038/nature08898
195. Burton DR, Weiss RA. AIDS/HIV. A boost for HIV vaccine design. Science (2010) 329(5995):770–3. doi:10.1126/science.1194691
196. Rizzardi GP, Harari A, Capiluppi B, Tambussi G, Ellefson K, Cuffreda D, et al. Treatment of primary HIV-1 infection with cyclosporin A coupled with highly active anti-retroviral therapy. J Clin Invest (2002) 109(5):681–8. doi:10.1172/JCI20452
197. Markowitz M, Vaida F, Hare CB, Boden D, Mohri H, Hecht FM, et al. The virologic and immunologic effects of cyclosporine as an adjunct to anti-retroviral therapy in patients treated during acute and early HIV-1 infection. J Infect Dis (2010) 201(9):1298–302. doi:10.1086/596166
198. Viskeoop N, Sankating S, Jansen CA, Roos MT, Otto SA, Schuitemaker H, et al. Short communication: no detrimental immunological effects of mycophenolate mofetil and HAART in treatment-naive acute and chronic HIV-1-infected patients. AIDS Res Hum Retroviruses (2005) 21(12):991–6. doi:10.1089/aid.2005.21.991
199. Hennessey EL, Parker AE, O’Neill LA. Targeting toll-like receptors: emerging therapeutic? Nat Rev Drug Discov (2010) 9(4):293–307. doi:10.1038/nrd3203
200. Hedelaty M, Netea MG, Reazai N. Targeting of toll-like receptors: a decade of progress in combating infectious diseases. Lancet Infect Dis (2011) 11(9):702–12. doi:10.1016/S1473-3099(11)70099-8
201. Tabb B, Morcrook DR, Trubey CM, Quinones OA, Hao XP, Smedley J, et al. Reduced inflammation and lymphoid tissue immunopathology in rhesus macaques receiving anti-tumor necrosis factor treatment during primary simian immunodeficiency virus infection. J Infect Dis (2013) 207(6):880–92. doi:10.1093/infdis/jjt463
202. Bissonnette R, Papp K, Maari C, Yao Y, Robbie B, White WL, et al. A randomized, double-blind, placebo-controlled, phase I study of MEDI-545, an anti-tnf-alfa monoclonal antibody, in subjects with chronic psoriasis. J Am Acad Dermatol (2010) 62(3):427–36. doi:10.1016/j.jaad.2009.05.042
203. Muller JT, Wallace DJ, Petri M, Kirou KA, Yao Y, White WL, et al. Safety profile and clinical activity of sifalimumab, a fully human anti-tnf-alpha monoclonal antibody, in systemic lupus erythematosus: a phase I, multicentre, double-blind randomised study. Rheumatology (2011) 50(11):1905–13. doi:10.1093/ard/rrr1485
204. Gringeri A, Musico M, Herrmann P, Bentwich Z, Cusini M, Bergamasco A, et al. Active interferon-alpha immunization: mechanisms of action and current perspectives. J Leukoc Biol (2010) 87(6):1301–15. doi:10.1189/jlb.0209211
a European-Israeli, randomized, double-blind, placebo-controlled clinical trial in 242 HIV-1–infected patients (the EURIS study). J Acquir Immune Defic Syndr Hum Retrovirol (1999) 20(4):358–70. doi:10.1097/00042360-199904010-00006

215. Tavel JA, Huang CY, Shen J, Mc-Calf JA, Dewar R, Shah A, et al. Interferon-alpha produces significant decreases in HIV load. J Interferon Cytokine Res (2010) 30(7):461–4. doi:10.1089/jir.2009.0090

216. Kovacs JA, Deyton L, Davey R, Falloon I, Zunich K, Lee D, et al. Combined zidovudine and interferon-alpha therapy in patients with Kaposi sarcoma and the acquired immunodeficiency syndrome (AIDS). Ann Intern Med (1989) 111(4):280–7. doi:10.7326/0003-4819-111-4-280

217. Pesce A, Taillan B, Rosenthal E, Garnier G, Vinti H, Dujardin P, et al. Opportunistic infections and CD4 lymphocytopenia with interferon treatment in HIV-1-infected patients. Lancet (1993) 341(8860):1597. doi:10.1016/0140-6736(93)90736-Z

218. Landau A, Batisse D, Duong Van Huyen JP, Piketty C, Bloch F, Pouloux G, et al. Efficacy and safety of combination therapy with interferon-alpha2b and ribavirin for chronic hepatitis C in HIV-infected patients. AIDS (2000) 14(7):839–44. doi:10.1097/00002030-200005050-00010

219. Arizcorreta A, Marquez M, Fernandez-Gutierrez C, Guzman EP, Brun F, Rodriguez-Iglesias M, et al. T cell receptor excision circles (TRECs), CD4+, CD8+, and their CD45RO+ and CD45RA+ subpopulations in hepatitis C virus (HCV)-HIV co-infected patients during treatment with interferon alpha plus ribavirin: analysis in a population on effective antiretroviral therapy. Clin Exp Immunol (2006) 146(2):270–7.

220. Cepeda RJ, Williams FM, Ishimori ML, Weisman MH, Reveille JD. The use of anti-tumour necrosis factor therapy in HIV-positive individuals with rheumatic disease. Ann Rheum Dis (2008) 67(5):710–2. doi:10.1136/ard.2007.081513

221. Bisoendial RJ, Stroes ES, Kastelein JJ, Tak PP. Targeting cardiovascular risk in rheumatoid arthritis: a dual role for statins. Nat Rev Rheumatol (2010) 6(3):157–64. doi:10.1038/nrrheum.2009.277

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