Virological and Immunological Impact of Tuberculosis on Human Immunodeficiency Virus Type 1 Disease

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Unlike other opportunistic infections associated with human immunodeficiency virus (HIV) type 1, tuberculosis (TB) occurs throughout the course of HIV-1 infection, and, as a chronic infection, its impact on viral activity is sustained. In dually infected subjects, HIV-1 load and heterogeneity are increased both locally and systematically during active TB. Studies over the past decade have indicated that Mycobacterium tuberculosis (MTB) infection supports HIV-1 replication and dissemination through the dysregulation of host cytokines, chemokines, and their receptors. Furthermore, concentrations of HIV-1 inhibitory chemokines are limited during TB and at sites of MTB infection. Cumulatively, these data indicate that TB provides a milieu of continuous cellular activation and irregularities in cytokine and chemokine circuits that are permissive of viral replication and expansion in situ. I address new research that has identified the basis for the augmentation of HIV-1 replication during TB and discuss potential immunotherapies to contain viral expansion during TB.

Worldwide, tuberculosis (TB) is the most frequent coinfection in subjects with human immunodeficiency virus HIV) type 1 infection [1]. HIV-1 infection remains the most common risk factor for the development of active TB [2]. Both reactivation of a latent Mycobacterium tuberculosis (MTB) infection and progressive primary TB are substantially more common in HIV-1–infected subjects [3]. The resurgence of TB has been attributed, in part, to the HIV-1 epidemic in the United States [4] and other developed countries, and, in developing countries, 60%–70% of TB cases occur in HIV-1–infected individuals [1, 5, 6]. There is a mutual interaction between HIV-1 and MTB infection; on the one hand, HIV-1 infection predisposes to the development of active TB, and, on the other hand, the course of HIV-related immunodeficiency is worsened by active MTB infection. The present article focuses mainly on the impact of TB on progression of HIV-1 disease, investigates the known and possible mechanisms for increased HIV-1 activity, and suggests possible methods to attenuate viral activation in subjects with dual infection.

CLINICAL ASPECTS OF TUBERCULOSIS IN HIV-1-INFECTED SUBJECTS

Unlike other opportunistic infections (OIs), active TB occurs throughout the course of HIV-1 disease. Mean CD4 cell counts of HIV-1–infected subjects at the time of development of pulmonary TB are, in general, higher (300–400 cells/μL) than in other OIs (<200 cells/μL) [7]. It appears that, in HIV-1–infected subjects with higher CD4 cell counts (≥500 cells/μL), pulmonary TB has the clinical and immunological features of reactivation TB in HIV-1–uninfected individuals, whereas the features of progressive primary TB are more common in HIV-1–infected patients who have CD4 cell counts <500 cells/μL [8] (figure 1). As expected, disseminated and extrapulmonary TB occur more frequently in HIV-1–infected subjects with low CD4 cell counts (<200 cells/μL) [11, 12]. With the progression of immunodeficiency, features of poor granuloma formation pre-
Figure 1. Relationship of human immunodeficiency virus (HIV) load and CD4 cell count to one another during HIV-1 and tuberculosis (TB) coinfection and to mortality and the clinical form of pulmonary TB. The correlation between HIV-1 load and CD4 cell counts was displaced significantly in patients with HIV-1/TB, compared with that in patients with HIV-1 alone [9] (author’s unpublished data). The relative risk of death increased in patients with HIV-1/TB who had CD4 cell counts $\geq 200$ cells/$\mu L$ [10]. Gray, reactivated pulmonary TB; black, primary pulmonary TB, including progressive primary.

dominate at sites of MTB infection [13]. The rates of positive mycobacterial smear samples and culture of clinical samples from patients who are coinfected with HIV-1 and TB depend on the degree of immunodeficiency [13].

Regardless of the time of occurrence and form of disease, pulmonary TB in HIV-1–infected subjects appears to remain as responsive to antituberculous chemotherapy as that in HIV-uninfected subjects [14], except in patients with advanced HIV-1 disease, in whom extrapulmonary and/or disseminated TB are often present concomitantly [5]. Compared with HIV-seronegative patients with TB, patients with pulmonary TB who are coinfected with HIV-1 have similar times to conversion from positive to negative of their sputum cultures [15], and the rates of relapse of TB have not been higher with the administration of standard rifampicin-containing regimens [16]. Relapse rates are higher with increasing age, when treatment compliance is poor, and with substandard chemotherapy. The transmission rates of MTB infection among household members of sputum smear–positive HIV-1/TB and HIV-uninfected patients are similar (C. Whalen, unpublished data) [17]. Furthermore, it has been clearly shown that preventive chemotherapy is successful in HIV-infected skin test–positive subjects [18, 19]. These data implicate that adequate cellular immunity (manifested by positive skin-test reactivity) in the presence of prolonged antituberculous preventive chemotherapy is effective. More recent studies have indicated that even a shorter course (i.e., 3 months) of combination (isoniazid, rifampicin, and pyrazinamide) preventive chemotherapy of skin-test–re-active, HIV-1–infected subjects confers protection against the development of active TB (for up to 3 years) [20]. The results of a randomized trial of a 12-month regimen of isoniazid with a 2-month regimen of pyrazinamide and rifampin confirmed a similar efficacy of outcome in the prevention of TB in HIV-1–infected subjects [21] and provided further basis for the present Centers for Disease Control and Prevention recommendations [22].

The course of HIV-1 infection is accelerated subsequent to the development of TB (figure 1). Both the relative risk of death and rates of the development of new OIs were increased in HIV-1/TB coinfection, compared with CD4 cell–matched HIV-1–infected control subjects [23]. The validity of these findings has been questioned in one analysis [24]. Of interest, in a recent prospective study of patients with HIV-1/TB coinfection, TB was found to exert its most significant effect on lowering survival rates in subjects with more preserved immunological status (i.e., CD4 cell counts $>200$ cells/$\mu L$) [10]. Of note, at least 50% of TB cases in HIV-1–infected subjects occur in those with CD4 cell counts $>200$ cells/$\mu L$ [8]. Therefore, the possible impact of TB on HIV-1 disease is substantial.

**IMPACT OF TB ON HIV-1 REPLICATION AND HETEROGENEITY**

A number of studies have indicated that the development of TB is associated with increased HIV-1 replication. Both HIV-1 load and heterogeneity appear to be affected by MTB infec-
tion. Goletti et al. [25] first showed that virus load was increased in serum samples from HIV-1–infected patients at the time of diagnosis of TB, compared with serum samples obtained before diagnosis. Similarly, in a survey of purified protein derivative (PPD) skin-test–positive HIV-1–infected subjects who were evaluated for preventive chemotherapy [26], HIV activity was shown to be enhanced at the time of diagnosis of TB [9] and was sustained in a subgroup of patients. In the same study, when patients with HIV-1/TB coinfection were compared with CD4-matched and “ill” HIV-infected subjects without TB, virus load was found to be significantly higher only in those subjects with CD4 cell counts “in normal range” (i.e., $\geq 500$ cells/µL). However, compared with HIV-1–infected, asymptomatic (PPD skin-test–positive) subjects, both plasma virus load and cell (peripheral blood mononuclear cell [PBMC])–associated HIV-1 activity were higher across all CD4 cell counts, although differences were most prominent at CD4 cell counts $>500$ cells/µL [9]. Therefore, overall, the impact of TB on HIV-1 replication appears to be most significant at times when CD4 cell counts are preserved. It must be pointed out that the development of other OIs is also associated with increased viral activity [27, 28]. However, because other OIs commonly occur with CD4 cell counts $<200$ cells/µL, their significance in inducing the progression of HIV-1 disease is harder to appreciate. The chronic nature of active MTB infection needs to be considered in sustained viral activity in patients coinfected with HIV-1/TB. By contrast, the impact of acute events, such as vaccinations, on viral replication (regardless of CD4 cell count) is transient [29].

Increased systemic immune activation in HIV-1/TB coinfection [30] underlies, at least in part, enhanced virus load in dually infected patients. However, increased HIV-1 production can be clearly shown at sites of MTB infection as well [31, 32]. Nakata et al. [31] demonstrated increased HIV-1 load in bronchoalveolar lavage (BAL) fluid from TB-involved, compared with uninvolved, lungs of patients with HIV-1/TB coinfection. Another form of TB that is particularly prevalent in HIV-1–infected patients is pleural TB [33]. Pleural TB accounts for up to 10% of TB in Africa [33]. Although pleural TB in HIV–uninfected patients is self-resolving, in HIV-1–infected patients it is often progressive, and the pleural fluid remains culture positive for MTB for prolonged periods of time [34]. In HIV-1–infected patients with pleural TB, increased HIV-1 activity was demonstrable in both pleural fluid (acellular) and pleural mononuclear cells (cellular), compared with their corresponding systemic compartments [32].

Studies of HIV-1 heterogeneity have corroborated the effects of TB on HIV-1 replication. In a CD4 cell–matched cohort of patients with HIV-1 who were infected with TB versus those who were not, increased systemic HIV-1 heterogeneity was found in dually infected patients [35]. Distinct quasi species were found to be more frequent in patients with both HIV-1 and TB, as opposed to HIV-1–infected patients without TB. Nakata et al. [31] demonstrated increased heterogeneity in TB-involved, compared with uninvolved, lungs of HIV-1–infected patients with pulmonary TB. Using the pleural model of active MTB infection, Collins et al. [36] demonstrated compartmentalization of HIV-1 quasi species and cross-talks between HIV-1 systemically and in the pleura (i.e., sites of MTB infection). A trend toward higher HIV-1 heterogeneity of pleural, compared with systemic, isolates was also shown. More recently, these investigators have shown an association between expanded HIV-1 heterogeneity and enhanced viral fitness (E. J. Arts, M. E. Quinones-Mateu, K. R. Collins, G. Vanham, personal communication). Conceivably, HIV-1 isolates at sites of active MTB infection may leak into the circulation and contribute to overall HIV-1 heterogeneity during TB. By contrast, acute increases in HIV-1 replication, such as that seen subsequent to vaccinations [29], are apparently not associated with increases in HIV-1 heterogeneity, which again indicates the importance of the timing of antigenic stimuli or local selection pressures on the expansion of HIV-1 quasi species.

Overall, it can be concluded that sites of active MTB infection in subjects coinfected with HIV-1/TB act as epifoci of HIV replication and evolution, independent of systemic HIV-1 activity. As long as these sites harbor active MTB infection, however, they contribute to systemic viral activity. How new viral set points are established by active MTB infection and how they affect the course of HIV-1 disease need to be investigated.

**TRANSCRIPTIONAL ACTIVATION OF HIV-1 DURING TB**

Both systemic immune activation [30] and the local cytokine milieu at sites of MTB infection [37] have been implicated in enhanced HIV-1 activity in patients with both HIV-1 and TB (figure 2A). During TB, excess proinflammatory cytokines, such as tumor necrosis factor (TNF)–α [38], which has been clearly shown to induce viral replication [39], may be critical to the expansion of virus burden. The interaction of MTB with mononuclear phagocytes induces the expression of TNF-α before [40] and at the time of [41] phagocytosis of the bacilli and on exposure to MTB protein [42] and nonprotein constituents [43]. In patients coinfected with HIV-1/TB, enhanced circulating TNF-α activity during active TB correlates with HIV activity [44]. Furthermore, the sustained circulation of TNF-α levels during the treatment of TB has been associated with persistent viral activity in patients coinfected with HIV-1/TB [45]. In vitro, the neutralization of TNF-α incompletely but significantly reduced HIV-1 production by HIV-1–infected monocytes in response to mycobacterial PPD [46]. TNF-α–induced HIV replication is mediated predominantly through...
Figure 2. Proposed mechanisms for propagation of human immunodeficiency virus (HIV) type 1 by macrophages (MPs) and monocytes (MNs) at sites of active *Mycobacterium tuberculosis* (MTB) infection. 

A, MTB-infected MPs transcriptionally activate HIV-1 (I) and/or cause new rounds of HIV-1 infection (II) in CD4 T cells and MNs and/or transactivate HIV-1 replication in newly recruited, latently infected CD4 T cells (III). 

B, At sites of active MTB infection, the differentiation of MNs to dendritic cells (DCs) may be conducive to the transmission of HIV-1 to CD4 T cells. The differentiation of MNs into MPs may allow the establishment of latent HIV-1 infection. ICAM, intercellular adhesion molecule; MCP, monocyte chemotactic protein; MIP, macrophage inflammatory protein; TNF, tumor necrosis factor.

the increased activation of NFκB [39], which is induced in mononuclear cells both by MTB infection in vitro and during TB in vivo [47]. The long terminal repeat (LTR) of HIV contains 2 NFκB sites, and NFκB, either alone [48] or in concert with other transcription factors [49], is critical to the transcriptional activation of HIV-1. Recent research has suggested that the activation of mitogen-activated protein (MAP) kinase pathways are also important in HIV-1 replication. Both NFκB dependent and independent effects of MAP kinase on HIV-1 replication have been described elsewhere [50]. In particular, the p38 MAP kinase pathway has been found to be critical in HIV-1 replication in both CD4 T cells [51] and mononuclear phagocytes [50], and the inhibition of p38MAP kinase blocked HIV-1 production [50]. Proinflammatory cytokines interleukin (IL)–1β and TNF-α activate p38 MAP kinase and the HIV-1 LTR [52], and, as noted, these cytokines are up-regulated by the MTB infection of mononuclear phagocytes [53, 54] and during TB [38]. Our recent observations have suggested that p38 MAP kinase is activated in the lung mononuclear cells of patients with TB after stimulation by mycobacterial PPD and by MTB infection of lung mononuclear cells from healthy subjects (author’s unpublished data). Whether the inhibition of p38 MAP kinase inhibits HIV replication in situ during TB needs to be investigated, because inhibitors of signaling pathways may become therapeutic options in clinical practice.

Recent data have indicated a major role for the β chemokine, monocyte chemotactic protein (MCP) 1, in the activation of HIV-1. Unlike other β chemokines, MCP-1 is a ligand for CCR2 [55], rather than the critically important HIV-1 coreceptor CCR5 [56]; thus, its role in the inhibition of HIV-1 entry is limited. MCP-1 activates HIV-1 replication in vitro [57], and MCP-1 expression is up-regulated by the HIV-1 transactivator protein tat [58] and has been associated with higher circulating HIV-1 levels in advanced disease [57]. MCP-1 production is up-regulated during TB [59], and its levels are higher in BAL fluid obtained from patients with pulmonary TB than in fluid from healthy subjects [60]. Furthermore, MTB infection of lung macrophages from healthy subjects induces MCP-1 [60]. In the model of pleural TB in patients coinfected with HIV-1/TB, we have found that the increase in HIV-1 transcriptional activity at sites of MTB infection (i.e., pleura) was associated with increased concentrations of both TNF-α and MCP-1 [32]. TNF-α and MCP-1 may act in concert to enhance viral replication, and whether their expression is codependent is not known.

Whether dual HIV-1 and MTB infection of the same mononuclear phagocyte particularly predisposes to viral activation is
not known. The frequency with which this phenomenon occurs in vivo is difficult to establish. However, the sequential infection of in vitro–cultured macrophages with MTB, but not with other mycobacteria, and HIV-1 led to productive HIV-1 infection and successful transmission to T cells [61].

CELLULAR ACTIVATION AND ORIGINATION OF HIV-1 FROM MONONUCLEAR CELLS IN TB

Activated mononuclear cells expressing HLA-DR are the most productive source of HIV-1 replication in vivo [62]. Host cell-surface proteins [63, 64], including HLA-DR [65], are incorporated into the envelope of HIV-1 as it buds from either macrophages or lymphocytes [66]. Mononuclear cell activation is a feature of active TB both systemically [30] and at sites of MTB infection [67]. HIV-1–infected patients with pulmonary TB, compared with HIV-1–infected control subjects with no OIs, have increased numbers of plasma virions with HLA-DR [65]. Pleural fluid from patients coinfected with HIV-1 and pleural TB contains high amounts of HLA-DR–reactive virions (when compared with their plasma) [68], which possibly indicates expanded viral production by activated mononuclear cells in situ. Of interest, viral transcription was up-regulated by major histocompatibility class II transactivator (CIITA) in T cell lines infected with HIV-1 [69]. Because CIITA is key in the regulation of HLA-DR expression [70], it is possible that the activation of this common transcriptional mechanism underlies the success of a productive HIV-1 infection in activated mononuclear cells [69]. These data suggest that the transcription of HIV-1 may be facilitated in HIV-1–infected cells that are HLA-DR positive at sites of infection. Recent studies have shown that the presence of HLA-DR within the viral envelope enhances HIV-1 infectivity [71]. Although the specificity of this observation is not entirely clear at present, it is intriguing to speculate that active production of DR-containing virions leads to the productive infection of uninfected mononuclear cells that are newly recruited to sites of MTB infection. Under this scenario, the expansion of HIV-1 will be sustained as long as MTB infection, and thereby the recruitment and activation of HIV-1–uninfected mononuclear cells, is maintained.

NEW ROUNDS OF HIV-1 INFECTION DURING TB

During TB, dysregulations in β chemokines [72] and their receptors [73] have been described that may contribute to enhanced viral dissemination. Of interest, the induction of HIV-1 inhibitory β chemokines macrophage inflammatory protein (MIP)–1α and RANTES by MTB was limited in HIV-1–infected patients who were coinfected with TB, compared with those not coinfected with TB [8]. On the other hand, the expression of CCR5 mRNA was higher in patients coinfected with HIV-1/TB than in patients with TB but not HIV-1, and higher amounts of CCR5 were found on the CD4 T cells in PBMCs of patients coinfected with HIV-1/TB [8]. The increase in HIV-1 activity in the pleural compartment of patients coinfected with HIV-1/TB was found in association with the enhanced expression of CCR5 mRNA by pleural mononuclear cells and low levels of the HIV-1–inhibiting β chemokines RANTES and MIP-1α in situ [32]. The β chemokine MCP-1 may be particularly involved in the process of the recruitment of monocytes and memory T cells to sites of MTB infection [55]. Levels of MCP-1 were higher in BAL fluid samples from patients with pulmonary TB [60] and in the pleural fluid of both HIV-1–infected and –uninfected patients [32]. As the maturation of newly recruited monocytes continues, there is a loss of CCR2 [74] and increased expression of CCR5. We have found an increased expression of CCR5 on both CD4 T cells and CD14 reactive cells (macrophages) in pleural fluid from patients coinfected with HIV-1/TB (author’s unpublished data), which indicates that, at sites of MTB infection, both cell types are potentially targeted by new rounds of HIV-1 infection, particularly in the face of limited β chemokine levels (figure 2A). Whether dysregulations in chemokines and the increased expression of CCR5 at sites of MTB infection in fact promote new rounds of HIV-1 infection needs to be substantiated. Also, whether these dysregulations contribute to the dissemination of HIV-1 infection systemically—for example, in the lymph nodes—needs to be determined.

REACTIVATION OF LATENT HIV-1 BY MTB

We have previously reported that MTB and PPD transcriptionally activate latent HIV-1 in alveolar macrophages from HIV-1–infected patients [75]. Although MTB and PPD were sufficient to induce HIV-1 transcription, the presence of lymphocytes was necessary to induce the production of virions by mycobacterium-stimulated macrophages. Others have confirmed the need for exposure to lymphocytes in optimal HIV-1 production by mononuclear phagocytes from patients with TB [76]. On the other hand, because monocytes that are latently infected with HIV-1 are recruited to sites of MTB infection, they may be particularly prone to viral activation. The predominant isoform of the transcription factor CCAAT/enhancer binding protein β (c/EBPβ) induced by MTB in monocytes is the HIV-1 LTR stimulatory isoform; therefore, HIV-1 replication is activated in these cells by exposure to MTB in situ [77]. Thus, during TB in HIV-1–infected subjects, transcriptional activation may occur either in the more mature, latently infected resident alveolar macrophages or in the smaller fraction of latently infected immature alveolar macrophages (blood monocytes) newly recruited to sites of MTB infection.

During HIV-1 infection, most HIV-1 originates from short-
lived virus-producing CD4 cells that may require activation by surface interactions with mononuclear phagocytes [78]. In microenvironments where lymphocytes and macrophages are in proximity, such as in the lymph nodes of HIV-1–infected subjects or during coinfections such as TB, the activation of CD4+ T cells by mononuclear phagocytes is likely. Recently, we have found that monocytes and macrophages infected with MTB, but not with *M. avium intercellulare*, induce HIV-1 LTR activity in lymphocytes (author's unpublished data). MTB products such as lipoarabinomannan are also potent in the activation of HIV-1 transcription in T cells [79] and T cell lines [80]. Thus, the induction of viral replication in latently infected T cells by MTB-infected mononuclear phagocytes and MTB constituents is likely. Whether the transactivation of HIV-1 in CD4 T cells through interaction with MTB-infected mononuclear phagocytes is important to the loss of viral latency at sites of active MTB infection during TB is presently speculative and needs to be further established.

**ESTABLISHMENT OF LATENT HIV-1 RESERVOIRS AT SITES OF MTB INFECTION**

Studies of BAL cells from the MTB-involved lungs of patients with active TB show an intense macrophage and lymphocyte alveolitis that TB-uninvolved lungs [67]. Up to 20% of the alveolar macrophages have features indicating “immaturity,” which suggests an ongoing recruitment of blood monocytes to sites of infection. The recruitment of immature monocytes to MTB-infected pulmonary or pleural sites, and their increased susceptibility to productive HIV-1 infection [81], may well be conducive to the establishment of HIV-1 reservoirs in situ. The differentiation of monocytes along the macrophage lineage is associated with a switch in expression of an HIV-1–stimulatory isoform of c/EBPβ to an HIV-1–inhibitory isoform [77]. The same stimulatory isoform is present in pulmonary macrophages during TB (which, as noted, are partly immature) [82]. With the maturation of these immature macrophages at sites of MTB infection, the inhibitory isoform of c/EBPβ becomes predominant, and latency becomes possible. Macrophages are long-lived cells and therefore may act as reservoirs of latent HIV-1 in the tissues. Macrophages are resistant to Fas-mediated apoptosis through the down-regulation of antiapoptotic molecules [83]. The enhanced survival of HIV-1–infected macrophages may further allow the establishment of HIV-1 latency in situ. Furthermore, the abundance of some proinflammatory cytokines (e.g., IL-1) at sites of MTB infection may also induce the transcription factor Yin-Yang 1 [84], which is thought to be important in the repression of the HIV-1 LTR through the recruitment of histone deacetylase [85]. TB-related mechanisms of establishment of HIV-1 latency need to be studied further.

**OTHER POTENTIAL MECHANISMS OF HIV-1 EXPANSION DURING ACTIVE TB**

Functional and biochemical changes occurring concomitant with the maturation of mononuclear phagocytes will likely have consequences on HIV-1 disease in vivo. For example, the differentiation of newly recruited immature monocytes to dendritic cells (DCs) may affect the persistence of HIV-1 infection at sites of MTB infection. In vitro, monocyte-derived DCs were able to be infected by HIV-1 and transmitted HIV-1 efficiently to CD4 T cells [78, 86]. The transmission of HIV-1 by monocyte-derived DCs to CD4 T cells is dependent on the cellular activation of T cells and involves the interaction of surface molecules (e.g., CD40/CD40L and intercellular adhesion molecule/leukocyte function antigen–1) [78, 86]. A reversal of transmission—that is, from CD4 T cells to DCs—has also been shown [86]. The dynamics of the differentiation of monocytes to DCs may be particularly facilitated in the microenvironment of MTB-infected tissues under the influence of cytokines such as granulocyte macrophage colony-stimulating factor [37]. In addition, DCs may migrate to draining lymph nodes during MTB infection [87]. Therefore, DCs may play a central role in the transmission of HIV-1 to HIV-1–uninfected CD4 T cells, both at sites of MTB infection and remotely.

The programmed cell death (PCD) of T cells is increased at the time of diagnosis of TB in both HIV-1–infected and—uninfected patients with pulmonary TB [88, 89]. In patients coinfected with HIV-1/TB, T cell activation (as determined by HLA-DR expression) is expanded in both CD4 and CD8 cells. PCD is greater in DR-reactive CD4 T cells; 3%–5% of HLA-DR–positive CD4 T cells (compared with <1% of HLA-DR–negative CD4 T cells) undergo apoptosis (C. S. Hirsch, unpublished data). At least during early HIV-1 disease (CD4 cell count >200 cells/μL), HLA-DR–reactive CD8 T cells do not appear to be predisposed to apoptosis. Whether augmented CD4 T cell PCD during TB in patients coinfected with HIV-1/TB underlies the loss of immune responses directed to HIV-1 needs to be established.

**IMMUNOTHERAPEUTIC INTERVENTION OF HIV-1 ACTIVITY DURING TB**

Both in vivo and in vitro data have strongly supported a role for TNF-α in activating HIV-1 transcription. The predominant identification of TNF-α during HIV-1/TB coinfection has, to a certain extent, hindered the clarification of the role of other mechanisms that may be involved in the augmentation of HIV-1 activity in dually infected subjects. Overall immunotherapies directed at the inhibition of TNF-α have not substantially reduced viral activity, which indicates that other possible concomitant mechanism(s) are additive or synergistic in HIV-1 expansion with TNF-α. In a placebo-controlled study, use of
the proinflammatory cytokine inhibitor thalidomide in patients coinfected with HIV-1/TB was associated with higher viral replication and no consistent effect on TNF-α levels [90]. Of interest, an improvement in CD4 and CD8 T cell counts and enhanced lymphoproliferation to MTB antigens were noted. Weight gain and reduced febrile days were noted in an initial report on the use of thalidomide in patients coinfected with HIV-1/TB [91]. In a trial of a second cytokine inhibitor, pentoxifylline, decreased plasma HIV-1 RNA and serum β2 microglobulin were shown; however, trends in the inhibition of TNF-α and improvements in CD4 cell counts did not reach significant [92]. A double-blind, placebo-controlled study of the use of corticosteroids, which potently inhibit proinflammatory cytokines, in patients with HIV-1/TB has shown that, despite the down-modulation of TNF-α and some transient effects on CD4 cell counts, HIV-1 activity in the 2 arms of the study at 1 month were similar (C. Whalen, unpublished data). In a more recent placebo-controlled study that examined the safety of TNF receptor–Fc chimera (etanercept) in patients coinfected with HIV-1/TB, despite a 25% increment in CD4 T cells, virus loads of treated patients were not affected significantly [93]. Cumulatively, these data indicate that the initiation of immunotherapies directed at the reduction of TNF-α at the time of diagnosis of TB may not be effective in reducing viral activity. Because the average time to detection of MTB infection from the onset of symptoms is ~2 months, during which viral replication and dissemination presumably are sustained, the initiation of therapies against cellular activation, such as anti-TNF-α agents (at the time of diagnosis of TB), may not be effective. It is possible, however, that TNF-α is acting in concert with other molecules that transcriptionally up-regulate HIV-1, such as MCP-1 or other proinflammatory cytokines (above). It is also possible that downstream mediators activated by TNF-α may have independent modulatory effects on viral activity. Alternatively, other mechanisms (e.g., new rounds of HIV-1 infection) may work together with TNF-α to increase HIV-1 loads during dual infection. Last, it is possible that the inhibition of TNF-α abrogates the PCD of CD4 cells [94]; however, the improvement of CD4 cell counts in fact expands the pool of cells that efficiently produce HIV-1. Future research needs to be directed at better defining the interaction of HIV-1 and TB, to identify the immunopathogenesis of HIV-1 during co-conditions and potential strategies for treatment.

CONCLUSIONS

The importance of the copathogenesis of HIV-1 and TB as an area of intense investigation hinges on 2 fundamental premises: (1) the enormity of these intertwined pandemics for world health and (2) the bidirectional interaction between these 2 pathogens provides insights into the immunopathogenesis of either. The immunological and virological consequences of HIV-1 and MTB copathogenesis within the host with dual infection may provide a perceptible model for the study of the immunopathogenesis of HIV-1 in humans. In particular, areas such as the study of the mechanisms of HIV-1 latency and reactivation still lack in vivo correlates. Thus, further analysis of the multifactorial interaction between HIV-1 and MTB may lead to novel approaches to effective drug and immune interventions.

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