MINIREVIEW

HIV–Mycobacterium tuberculosis co-infection: a ‘danger-couple model’ of disease pathogenesis

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An interesting perspective from a multinational (Malaysia, India, Sweden, USA) consortium on the special challenges raised in the concurrent management of HIV/TB co-infection due to complex drug interactions, overlapping toxicities and tuberculosis-associated IRIS. Several hypotheses are presented on the reasons for this exacerbation of tuberculosis pathogenesis by HIV and vice-versa.

Keywords
co-infection; HIV; immunomodulation; PD-1; tuberculosis; virulence.

Abstract
Tuberculosis (TB) and human immunodeficiency virus (HIV) infection interfere and impact the pathogenesis phenomena of each other. Owing to atypical clinical presentations and diagnostic complications, HIV/TB co-infection continues to be a menace for healthcare providers. Although the increased access to highly active antiretroviral therapy (HAART) has led to a reduction in HIV-associated opportunistic infections and mortality, the concurrent management of HIV/TB co-infection remains a challenge owing to adverse effects, complex drug interactions, overlapping toxicities and tuberculosis-associated immune reconstitution inflammatory syndrome. Several hypotheses have been put forward for the exacerbation of tuberculosis by HIV and vice versa supported by immunological studies. Discussion on the mechanisms produced by infectious cofactors with impact on disease pathology could shed light on how to design potential interventions that could decelerate disease progression. With no vaccine for HIV and lack of an effective vaccine for tuberculosis, it is essential to design strategies against HIV–TB co-infection.

Introduction
The co-evolution of bacteria with their host has led to bidirectional evolutionary pressures, eventually leading to refinement of survival mechanisms in both species that culminate in symbiotic relationships (Vujkovic-Cvijin et al., 2013). Certain microorganisms, despite the co-evolution process, can cause life-threatening pathology and disease, especially in immunocompromised hosts (Kownhar et al., 2007; Muthu et al., 2006; Shankar et al., 2005, 2006a, b; Vignesh et al., 2008). Long before AIDS was first reported, it was known that measles virus could render individuals immunosuppressed (Coughlin et al., 2013), and that tuberculosis commonly occurred following an outbreak of measles. It is also known that following an episode of chickenpox (varicella zoster virus infection), secondary pulmonary bacterial infections can develop owing to an immunocompromised state engineered by herpes viruses (Dinleyici et al., 2012). In the individual host, the two pathogens, Mycobacterium tuberculosis and the HIV type 1 (HIV), appear to have great impact on each other, accelerating the deterioration of immune functions (WHO, 2008; Pawlowski et al., 2012). Tuberculosis remains a major global health menace and is the second most frequent cause of death due
to infectious disease worldwide. Tuberculosis is reported to be encountered by one-third of the global population, of which about 10% develop active tuberculosis. According to the latest World Health Organization (WHO) estimates, there were c. 9 million new cases and 1.4 million tuberculosis deaths during 2011. In 2011, HIV-positive individuals accounted for 1.1 million (13%) of the 8.7 million people who developed tuberculosis worldwide (WHO, 2011). Of the individuals with tuberculosis who were tested for HIV, 23% were positive in 2011 (UNAIDS, 2012). Today, at least one-third of the 34 million people who are HIV-positive worldwide are infected with latent tuberculosis. Individuals co-infected with TB/HIV are reported to have an c. 21–34 times higher risk of developing active tuberculosis than those without HIV infection (WHO, 2011).

*Mycobacterium tuberculosis* is a highly evolved complex organism that affects primarily the respiratory tract, although disseminated lymphohematogenous infection can occur in immunocompromised subjects (Ray et al., 2013). Acquisition of *M. tuberculosis* infection is predominantly via inhalation of aerosolized bacilli into the respiratory tract. The alveolar macrophages patrolling the airways and Langerhans cells (immature dendritic cells (IDCs)) of the mucosal lining of the airways pick the bacilli, and process them along the route of transit to the regional lymph nodes to initiate the adaptive immune responses. However, the tubercle bacilli prevent fusion of the phagosomal compartment with the lysosome and replicate successfully within this vesicular niche (Vandal et al., 2009). The exact mechanism behind their retention in phagosomes remains unclear, but might depend on evasion of the acidic barriers within the endosomal vesicle via the bacilli’s arabinogalactan mycolate lipoparabinomannan (LAM) complex (Wax-D)-enriched acid-fast cell-wall structures (Forrellad et al., 2013). Wax-D on the surface of the tubercle bacilli probably modifies the phagosome membrane and inhibits the trafficking processes that would normally enhance fusion of phagosomes with the lysosomal compartment (Dhiman et al., 2009; Forrellad et al., 2013). Bacterial establishment is also facilitated by exuberant accumulation of macrophages, fibroblasts, lymphocytes, DCs and neutrophils that form multinucleated giant cell-rich granulomas, which seek to limit replication of the bacilli (Dhiman et al., 2009). Nonetheless, *M. tuberculosis* persists within the granuloma, and any event that reduces the integrity of the granuloma will eventually reactivate the latent tuberculosis infection. This reactivation leads to lymphohematogenous dissemination, and onset of severe active tuberculosis marked by Ghon focus (involving hilar lymph nodes) and caseous necrosis, especially in the apical segment of lungs owing to poor air pumping mechanisms and lymphatic distribution (Tan et al., 2010).

HIV infection is acquired mainly via genital mucosal exposure where immature DCs pick the virus from mucosal sites, and disseminate the virus to the CD4+ coterie of T cells, eventually leading to the onset of T-cell depletion and opportunistic infections (OIs) and neoplasms (Kumarasamy et al., 2005; Vignesh et al., 2007). A handful of novel mechanisms have been described to account for the onset of immune dysfunctions in HIV disease both in vitro and in vivo (Che et al., 2010, 2012; Larsson et al., 2013; Vujkovic-Cvijin et al., 2013). Endogenous infections that alter the natural history of HIV disease are defined as cofactors of disease progression (Kumarasamy et al., 2005). Discussing the mechanisms produced by infectious cofactors with impact on the magnitude of disease pathology could shed light on how to design potential interventions that could decelerate disease progression. Hence, this minireview attempts to provide overall insight into the immunological events that could accelerate the development of each disease in the presence of co-infection, and also to describe the gaps in knowledge and the need for future research to develop preventive measures against HIV and tuberculosis.

**How does HIV contribute to exacerbation of *M. tuberculosis* infection?**

HIV-related dysfunction of local immune responses in HIV/TB co-infected individuals reduces the ability of granuloma, an organized structure comprising epithelioid macrophages surrounded by a rim of lymphocytes, to restrain tubercle bacilli, leading to their eventual multiplication and dissemination, thereby culminating in severe pathology (Lawn et al., 2002; Safi et al., 2003; de Noronha et al., 2008; Bezuidenhout et al., 2009). Furthermore, the exacerbation of tuberculosis pathology is linked to the increased replication of HIV at the sites of *M. tuberculosis* infection (Imperiali et al., 2001). HIV is known to replicate within activated CD4+ T cells and macrophages, which are known to accumulate at the site of granuloma (Imperiali et al., 2001). Elevated HIV-1 gag p24 levels and viral loads in bronchoalveolar lavage (BAL) fluid are detected in individuals with tuberculosis compared with individuals with no tuberculosis infection (Nakata et al., 1997). In addition, there is an increase in viral loads in pleural fluid compared with plasma among patients with pleural tuberculosis and greater HIV replication in activated macrophages co-infected with *M. tuberculosis* and HIV compared with HIV-infected macrophages, emphasizing that HIV replication is increased at sites of *M. tuberculosis* infection (Hoshino et al., 2002; Lawn et al., 2002).

The killing of CD4+ T cells by HIV within granuloma is associated with primary tuberculosis or reactivation of tuberculosis (Lawn et al., 2002; Diedrich & Flynn, 2011). Recent animal studies have demonstrated that monkeys co-infected with simian immunodeficiency virus strain mac251 (SIVmac251) and *M. tuberculosis* had fewer CD4+ T cells in granulomatous tissue than those with active tuberculosis alone (Diedrich et al., 2010). HIV-infected patients with lower CD4+ T-cell counts are more susceptible to tuberculosis than those with higher counts (Lawn et al., 2009; Diedrich et al., 2010). Furthermore, HIV/TB co-infected individuals have fewer CD4+ T cells in BAL fluid than those infected with tuberculosis alone (Kalsdorf et al., 2009).

The functionality of different immune cells such as macrophages and T cells are altered in co-infected individuals (Patel et al., 2007, 2009; Geldmacher et al., 2008, 2010; Kumawat et al., 2010). HIV/TB co-infected macrophages release lower levels of tumor necrosis factor-α (TNF-α) and induce less TNF-dependent apoptosis than...
those infected with *M. tuberculosis* alone (Patel et al., 2007, 2009; Kumawat et al., 2010) (Fig. 1). In addition, there is evidence for the negative impact of HIV on the ability of tuberculosis-specific T cells to contain bacterial establishment. For instance, there are fewer interferon-γ (IFN-γ)-producing *M. tuberculosis*-specific memory T cells following HIV infection in individuals with latent tuberculosis. Furthermore, studies have convincingly demonstrated lower IFN-γ and interleukin-2 (IL-2) production and proliferation by *M. tuberculosis*-specific T cells in HIV-infected individuals than in HIV-uninfected individuals with active tuberculosis (Hertoghe et al., 2000; Mendonça et al., 2007; Geldmacher et al., 2008). Recent findings showed that IL-10 production was significantly higher in HIV–TB co-infected individuals after *M. tuberculosis* stimulation, suggesting that chronic HIV infection could render the cell-mediated immunity (CMI) ineffective against *M. tuberculosis* (Geldmacher et al., 2010). Furthermore, there was less IL-2 production and higher macrophage inflammatory protein-1β (MIP-1β, also called CCL4) production by the *M. tuberculosis*-specific CD4+ T cells in HIV-infected vs. HIV-uninfected patients (Geldmacher et al., 2010), supporting the fact that HIV preferentially infects and depletes IL-2-producing CD4+ T cells and is partially inhibited from depleting MIP-1β-pro-

**Fig. 1** Proposed model of HIV/Mycobacterium tuberculosis co-infection: the ‘danger-couple’ model of disease pathogenesis. *Mycobacterium tuberculosis* and HIV have evolved to favor each other in facilitating disease pathogenesis. (a) *Mycobacterium tuberculosis*-infected resident alveolar macrophages produce increased levels of TNF-α, IL-1 and IL-6, leading to enhanced HIV replication (Kedzierska et al., 2003; Briken et al., 2004) and persistence within macrophages. Furthermore, HIV/M. tuberculosis-coinfected macrophages are less prone to undergo TNF-dependent apoptosis (Patel et al., 2007, 2009; Kumawat et al., 2010). (b) *Mycobacterium tuberculosis* increases the expression of CXCR4 in alveolar macrophages, favoring entry of only X4 viruses (Vanham et al., 1996; Wolday et al., 2005; Hoshino et al., 2004; Juffermans et al., 2001) potentially in chronic HIV infection. (c) Increased IDO levels and decreased tryptophan levels in primary tuberculosis has been shown to correlate with poor tuberculosis prognosis (Suzuki et al., 2012), and therefore the increased IFN-γ levels seen during primary tuberculosis and acute HIV infection might be associated with IDO-associated T-cell suppression, although prostaglandin E2 (PGE2) could upregulate IDO in DCs (von Bergwelt-Baildon et al., 2006). High expression of PD-1 in T cells of HIV/M. tuberculosis-coinfected individuals has also been shown (Jurado et al., 2012). In this context, *M. tuberculosis* could also foster anti-inflammatory attributes in DCs (Talaat et al., 2006), although the potential role of IDO in explaining this concept remains to be investigated. HIV infection induces expression of immune activation markers, CD38, CD70 and HLA-DR, weakening T-cell responses against *M. tuberculosis* antigens (Flynn & Chan, 2001; Hazenberg et al., 2003). Furthermore, high IL-10 and less IL-2 production in HIV/M. tuberculosis coinfection further explains the concept of diminished CMI responses against *M. tuberculosis* (Geldmacher et al., 2010). *Mycobacterium tuberculosis* Wax-D triggers IL-12 secretion by DCs and macrophages, facilitating the expansion of CD4+ Th1 cells, which in turn supports HIV persistence (not shown) (Briken et al., 2004). CXCR4, CX-chemokine receptor 4; DC, dendritic cell; IDO, indoleamine 2,3, dioxygenase; IFN-γ, interferon gamma; IL, interleukin; HLA-DR, human leukocyte antigen-DR; Mφ, macrophage; MTB, *Mycobacterium tuberculosis*; PD-1, programmed death-1; Th1, thymus-derived helper T cell; TNF-α, tumor necrosis factor alpha.
producing CD4+ T cells. In addition, Wax-D on the bacterial cell surface triggers IL-12 secretion by DCs and macrophages, facilitating the expansion of CD4+ Th1 cells, which in turn supports HIV establishment (Briken et al., 2004). HIV-1 also promotes the secretion of indoleamine 2,3 dioxygenase (IDO) a tryptophan-catabolizing enzyme required for T-cell suppression (Favre et al., 2010; Larsson et al., 2013; Planes & Bahraoui, 2013). A recent study has kindled interest in the role co-inhibitory molecules play in T-cell activation in HIV/TB co-infection. The study showed significantly higher expression of PD-1 on T cells from HIV-TB co-infected individuals than on T cells from tuberculosis patients and healthy controls (Jurado et al., 2012), further indicating that HIV could contribute to lessen CMI responses against tubercle bacilli (Fig. 1) by upregulating the expression of coinhibitory molecules on effector immune cells as described recently in a series of interesting in vitro (Shankar et al., 2011; Che et al., 2012; Larsson et al., 2013) and in vivo investigations (Velu et al., 2009). HIV infection could also induce expression of immune activation markers such as CD38, CD70, HLA-DR and CD45R0 to weaken T-cell responses against *M. tuberculosis* antigens (Flynn & Chan, 2001; Hazenberg et al., 2003) (Fig. 1).

**How does tuberculosis exacerbate HIV-1 infection?**

Co-infection with *M. tuberculosis* negatively impacts the HIV immune responses and this is demonstrated by a higher incidence of new AIDS-defining OIs in HIV/TB co-infected individuals (Pape et al., 1993). There appears to be high plasma viral load (PVL) (Goletti et al., 1996), and HIV replication is up-regulated in blood and pulmonary lymphocytes and alveolar macrophages ex vivo (Shattuck et al., 1993; Zhang et al., 1995; Goletti et al., 1996; Lawn et al., 2011) in HIV-infected individuals with active tuberculosis disease. The exacerbated HIV replication in alveolar macrophages, the primary targets for *M. tuberculosis*, has also been detected in the BAL from co-infected patients (Lawn et al., 2011).

HIV uses co-receptor CCR5 predominantly during the establishment and early in the course of infection, whereas as the disease progresses the use of CXCR4 becomes more frequent (Rosas-Taraco et al., 2006). *Mycobacterium tuberculosis* creates an environment accommodating the replication of CXCR4-tropic HIV by increasing the expression of CXCR4 in alveolar macrophages and suppressing entry of CCR5-tropic HIV, thereby creating a selective pressure for CXCR4-tropic HIV (Vanham et al., 1996; Wolday et al., 2005; Hoshino et al., 2004; Juffermans et al., 2001).

It has been established that HIV and *M. tuberculosis* infections in concert stimulate TNF-α production, which in turn has been shown to enhance HIV replication in macrophages (Kedzierska et al., 2003). *Mycobacterium tuberculosis* infection activates the suppressor of cytokine signaling 1 (SOCS1), an inducible host factor during HIV-1 infection that facilitates viral replication by inhibiting type-1 IFN antiviral signaling (Fenner et al., 2006). Apart from the effects on HIV replication, *M. tuberculosis* infection has also been shown to down-regulate the proinflammatory and antigen-presenting abilities, and activate the anti-inflammatory functions of DCs (Talaat et al., 2006). DC-mediated activation of T cells is reportedly impaired in HIV infection, and migration of DCs along with HIV contributes to efficient viral dissemination (Wang et al., 2009; Geldmacher et al., 2008; Geijtenbeek et al., 2000). Wax-D has also been implicated in the activation of HIV replication by enhancing TNF-α and IL-6 production by DCs (Briken et al., 2004), which could give rise to increased HIV-1 replication furthering immnosuppression. Here, we have proposed a ‘danger-couple’ model of HIV/*M. tuberculosis* co-infection (Fig. 1), whereby HIV-infected T cells become dysfunctional, eventually leading to the loss of intracellular killing abilities of macrophages harboring *M. tuberculosis*.

Simultaneously, the *M. tuberculosis*-infected macrophages containing LAM (Wax-D) produce increased levels of TNF-α, IL-1 and IL-6, leading to enhanced viral replication (Briken et al., 2004) and HIV persistence within macrophages. One recent theory is that HIV helps *M. tuberculosis* persist within the macrophages, facilitating increased synthesis of IFN-γ, which promotes secretion of IDO, a tryptophan-catabolizing enzyme, leading to T-cell inhibition, but this remains to be investigated. If IFN-γ levels have no association with IDO secretion by DCs, the role of prostaglandin E2 (PGE2) could be considered (von Bergwelt-Baildon et al., 2006) for potential investigation. By decreasing available tryptophan and producing tryptophan metabolites, such as kynurenine (Kyn), IDO inhibits T-cell functions and leads to immune suppression. Beguilingly, one recent study points to increased IDO levels and decreased tryptophan levels in primary tuberculosis and correlated the levels with poor tuberculosis prognosis (Suzuki et al., 2012) (Fig. 1).

**Reciprocal effects of HIV/*M. tuberculosis* on each other**

Several in vitro studies have demonstrated that phagocytosis of *M. tuberculosis* induces macrophage activation, and production of proinflammatory cytokines, namely TNF-α, IL-1β and IL-6 by macrophages, is known to enhance replication of HIV-1 (Molina et al., 1989; Weiss et al., 1989; Birx et al., 1990; Emilie et al., 1990; Lafeuillade et al., 1991; Herbein & Varin, 2010; Cozzi-Lepri et al., 2011). Growth of *M. tuberculosis* was observed to be significantly greater in HIV-1-infected monocyte-derived macrophages (MDMs) compared with that in HIV-1-negative cells (Imperiali et al., 2001). Also, adding TNF-α to HIV-1-infected MDMs induced a significant increase of *M. tuberculosis* growth, compared with cultures performed in the absence of the cytokine, whereas addition of TNF-α had no effect on *M. tuberculosis* growth in uninfected MDMs (Imperiali et al., 2001). In latent HIV-1-infected promonocytic cells, phagocytosis of *M. tuberculosis* induced viral production, and in acutely HIV-1-infected MDMs, *M. tuberculosis* growth was increased (Imperiali et al., 2001). Furthermore, HIV-1 infection induced a greater bacilli burden in co-infected cell cultures and specifically induced accelerated growth of *M. tuberculosis*; in turn, the bacteria induced the replication...
of HIV-1 (Pathak et al., 2010). The co-infection of HIV-1/TB synergistically decreased the viability of macrophages and increased levels of proinflammatory cytokines and this seemed to be specific to M. tuberculosis rather than other species of mycobacteria (Pathak et al., 2010).

Dual complications: clinical presentation and diagnosis of tuberculosis in HIV/ M. tuberculosis co-infection

The clinical presentation of tuberculosis in HIV/M. tuberculosis-coinfected individuals is known to vary according to the immune status, and atypical features usually observed include lower lobe involvement with a trend towards diffuse infection rather than cavitation (Aaron et al., 2004). In severely immunocompromised HIV-infected individuals, pulmonary basal involvement, hilar or mediastinal lymphadenopathies, and miliary tuberculosis are most commonly observed (Perlman et al., 1997). Diagnosis of active tuberculosis in HIV-infected individuals is challenging, because there are fewer tuberculosis bacilli in sputum specimens from individuals with HIV/TB co-infection than from HIV-uninfected patients with pulmonary tuberculosis due to markedly reduced transfer of bacilli in respiratory secretions (Mugusi et al., 2006; Padmapriyadarsini et al., 2011).

Extrapulmonary tuberculosis in HIV-positive individuals

The proportion of extrapulmonary tuberculosis (EPTB) has been reported to be higher among HIV-infected individuals than among the immunocompetent population (Sharma et al., 2005; Patel et al., 2011). EPTB is high significant in HIV being designated an AIDS-defining illness and occurs frequently and earlier than most other OIs and with high rates of mortality (Shanmuganathan et al., 2013). Several studies have demonstrated lymph nodes as the most common site of EPTB infection among HIV-infected individuals (Deivanayagam et al., 2001; Leeds et al., 2012; Shanmuganathan et al., 2013). According to a recent study, EPTB is the most common form of tuberculosis in HIV patients with low CD4+ T-cell counts, and the common presenting symptoms of EPTB include fever, weight loss and cough (Spalgaïs et al., 2013).

Tuberculosis and immune restitution inflammatory syndrome

Immune reconstitution inflammatory syndrome (IRIS) is an adverse consequence of the restoration of pathogen-specific immune responses in HIV-infected patients during the initial period of highly active antiretroviral treatment (HAART) (Kumarasamy et al., 2004). Although IRIS is associated with certain infectious and non-infectious conditions (Shankar et al., 2007), the morbidity associated with HIV/TB co-infection is significantly higher than for the other conditions. HIV-infected patients with low CD4+ T-cell counts ‘immunologically’ tolerate the presence of the tubercle bacilli as the host is unable to mount an inflammatory response (Shankar et al., 2008a, b). Tuberculosis-associated IRIS is considered critical in developing countries, where the proportion of HIV/TB IRIS is reportedly high, ranging from 10% to 43% (Breton et al., 2004; Shelburne et al., 2005; Murdoch et al., 2008; Haddow et al., 2012). Although the pathophysiology of IRIS is incompletely understood, sustained Th1 responses evident by increased IFN-γ responses against the mycobacterial antigens, followed by dysregulation of cytokine secretion and T-cell migration to the inflammatory site have been demonstrated (Bourgarit et al., 2006; Vignesh et al., 2013).

A recent study demonstrated the possible role of Th1 responses in the pathogenesis of TB-IRIS and showed that HIV-infected patients who develop TB-IRIS had higher Th1 responses to M. tuberculosis antigens before they began HAART, and that these responses are amplified after initiation of HAART (Vignesh et al., 2013). This mechanism could possibly be due to the higher mycobacterial load in patients who develop TB-IRIS, leading to a larger number of Th1 cells and also there might be acquired susceptibility to produce higher Th1 responses. This acquired susceptibility could be related to perturbations of innate immune responses that have been associated with TB-IRIS, such as elevated production of IL-18, a potent stimulator of Th1 responses, and CXCL10, a well-known chemoattractant for Th1 cells (Vignesh et al., 2013). This study also investigated the expression of CCR5 and CXCR3 expression on T cells and found an increased proportion of CCR5+ CD4+ T cells among patients with TB-IRIS (Vignesh et al., 2013). Elevated pre-HAART levels of TNF, high inflammation biomarker levels and significantly lower levels of antibodies to phenolic glycolipid (PGL-TB1) antigen existed in individuals who developed TB-IRIS than those who did not (Simoney et al., 2008; Boulware et al., 2011). A recent study indicated natural killer (NK) cell degranulation levels as a predictor for TB-IRIS among HIV/TB co-infected patients initiating HAART (Pean et al., 2012).

Management of HIV/TB co-infection – therapeutic considerations

The treatment modality for tuberculosis in HIV-infected individuals is the same as for HIV-uninfected, with the regimen of a four-drug intensive phase of 2 months, followed by 4 months of a two-drug regimen in continuation phase (Treatment of tuberculosis: Guidelines, WHO, 2010). Development of multi-drug resistant (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) is a challenge faced by healthcare providers when treating tuberculosis, especially in TB/HIV co-infected individuals. Two mechanisms have been suggested that link drug-resistant tuberculosis to HIV infection. One is tuberculosis drug malabsorption, especially with rifampin and ethambutol leading to treatment failure, the other being that drug-resistant strains might be less virulent and preferentially aid disease progression in HIV patients with a compromised immune system, as opposed to immune-competent individuals (Patel et al., 1995; Suchindran et al., 2009).

The antiretroviral drug regimen should be chosen on the basis of minimal drug interactions with the anti-tuberculosis
treatment (Londhey, 2009). Rifampicin is known to interact with non-nucleoside analogue reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs) (Varghese et al., 2013). Drug–drug interactions between rifampicin and NNRTIs leads to subtherapeutic levels of NNRTIs and subsequent treatment failure. Nevirapine is not recommended for individuals receiving rifampicin treatment for TB, where it reportedly decreases the serum concentration of nevirapine by about 50% (Riberas et al., 2001). Efavirenz is the drug of choice by reason of manageable drug–drug interactions, except in conditions such as pregnancy where it is contraindicated (Narita et al., 2000). To prevent drug–drug interactions while starting treatment with PIs with rifabutin, an alternative drug is recommended as it does not affect the serum concentrations of PIs (Sundaram et al., 2008). In HIV-infected individuals with tuberculosis, antituberculous treatment (ART) should be initiated during tuberculosis treatment regardless of CD4+ T-cell counts. Recent studies have clearly shown that initiation of ART 2 weeks after tuberculosis treatment is more beneficial than delaying ART for 8 weeks. Despite the increased incidence of TB-IRIS, this was shown to reduce mortality (Abdool Karim et al., 2010; Blanc et al., 2011; Havlir et al., 2011). However, these data are based on studies from countries with a high tuberculosis burden with limited resources and further data from large-scale multisite trials are warranted.

Conclusions

Conventionally, coinfections in HIV-infected individuals accelerate the disease progression (Shankar et al., 2008a, b). HIV/TB coinfection continues to be a dual threat to healthcare providers and represents a novel pathogenic scenario globally. Countries with limited resources are most affected with a high burden of both diseases, yet have strained healthcare budgets. The most logical and practical option to combat the coinfections would be to develop an effective combined vaccine for both HIV/TB, although currently no effective vaccine exist for either HIV or tuberculosis. Research priorities that need to be urgently addressed include further understanding of the immunopathogenic mechanisms underlying the mutual exacerbations of tuberculosis and HIV disease to combat them effectively and optimizing the treatment modalities to minimize complications such as TB-IRIS and drug–drug interactions. The following scientific objectives are needed for effective integration of knowledge on the HIV/TB coinfection: developing standard in vitro and in vivo models for studying the mechanisms of coinfection, employing mathematical and computer-based simulation models to understand the immune responses better and regulation of T-cell differentiation during coinfection. Moreover, an integrated approach to the two infections, based on drafting effective policies to contain both, is essential.

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