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Persistent High Mortality in Advanced HIV/TB Despite Appropriate Antiretroviral and Antitubercular Therapy: An Emerging Challenge

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Abstract

Approximately 1.1 million, or 13%, of all TB cases in 2012 were co-infected with HIV, and in some African countries, such as Botswana and Swaziland, 60–80% of TB cases are co-infected with HIV. Effective therapies for both HIV and TB exist, yet patients presenting with TB and advanced HIV still experience high rates of morbidity and mortality despite initiation of both anti-tubercular and anti-retroviral therapy (ART). Previous reviews and research have focused largely on TB-associated immune reconstitution inflammatory syndrome (TB-IRIS) as a type of complicated outcome on ART in advanced HIV/TB, but recent data indicate that immunologic failure despite suppressive ART is associated with early mortality. In this review, we examine recent findings regarding early mortality in HIV/TB and emerging concepts in the pathophysiology of TB-IRIS, in order to provide an integrated view of factors determining outcomes in coinfecting people as well as highlight key needs for future research and therapeutic development.

Keywords

Tuberculosis; HIV; Mortality; Immune reconstitution inflammatory syndrome; Immunology

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Conflict of Interest

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Human and Animal Rights and Informed Consent

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Introduction

The World Health Organization (WHO) estimates that in 2012 there were nearly 9 million new cases of tuberculosis (TB), leading to 1.3 million TB-related deaths (1). Approximately 1.1 million, or 13%, of all TB cases in 2012 were co-infected with HIV, and in some African countries, such as Botswana and Swaziland, 60–80% of TB cases are co-infected with HIV (1). HIV infection leads to a markedly increased risk of active TB (2), manifesting not only in the setting of advanced immune deficiency, but also in the initial months after HIV acquisition and persisting even as CD4 + T (CD4) cell counts rise on antiretroviral therapy (ART) (3). A major goal of the Stop TB Strategy was to halve, from 1990 levels, TB-related deaths by 2015 (4). Unfortunately, this goal is unlikely to be met in settings with a high burden of HIV/TB (1). In addition to improved HIV testing, infection control, and isoniazid preventive treatment, decreasing TB-related deaths among HIV/TB co-infected individuals depends on improving treatment outcomes. A particular challenge is that, among patients presenting with TB and very advanced HIV, mortality rates remain substantial despite initiation of both anti-tubercular therapy and ART (5). As efforts to increase availability of ART in the developing world continue to ramp up, a critical emerging challenge is the persistent high mortality in TB/HIV coinfecting people despite appropriate anti-TB and antiretroviral treatment.

Recently, results of international clinical trials evaluating timing of ART initiation in HIV/TB have highlighted the importance of the CD4 count in determining ART timing in individuals with advanced disease (6–8). These data indicate that patients with advanced HIV/TB are both in need of rapid ART initiation and immune recovery and at risk of pathologic inflammation due to the TB-immune reconstitution inflammatory syndrome (TB-IRIS) (9–12). Concerns about rapid immune recovery after ART initiation have led to numerous reviews on TB-IRIS (13–16) and clinical trials evaluating immunomodulatory therapy (e.g., corticosteroids) administered at the time of ART initiation to prevent it. However, while paradoxical TB-IRIS is seen in approximately 15% of those with HIV/TB who start ART, the syndrome is rarely fatal (17). Furthermore, a recent study suggested that mortality among people initiating ART and TB therapy with advanced HIV/TB is strongly associated with overt failure to recover CD4 cells and effector cellular immune function despite virologic suppression (5). This indicates that in the care of patients with advanced HIV/TB, the greatest risk is immunologic failure. Thus, a dominant focus on preventing TB-IRIS could increase mortality risk if so doing leads to inhibition of critical immune function important to survival. “Immunological failure” on ART in advanced HIV/TB also suggests that new interventions focusing on immune enhancement to prevent mortality in advanced HIV/TB should be investigated.

In this review, we examine how immunologic response to ART relates to clinical outcomes among HIV/TB coinfecting individuals. The goal of this review is to focus on emerging concepts that will inform current practice and highlight key needs for future research and therapeutic development aiming to promote safe and effective immune recovery on ART in patients with advanced HIV/TB.

Pathogen-specific immune function to *M. tuberculosis* – initial loss and heterogeneous recovery after ART initiation

Epidemiologic studies have demonstrated that patients with HIV manifest an increased risk of TB in the initial months after HIV seroconversion (2). This finding suggests that immune function related to control of *Mycobacterium tuberculosis* can be lost very early after HIV acquisition, well before global CD4 depletion. Geldmacher et al experimentally evaluated this association and demonstrated that IL-2 producing *M. tuberculosis*-specific T cells, which produce interferon- γ (IFN γ) and are considered critical to pathogen control (18), are particularly susceptible to HIV infection and are dramatically reduced within months after HIV infection (19). Protective immune function is further impaired during HIV disease progression, as the risk of TB increases in a somewhat dose-dependent manner as CD4 cell counts decline (3, 20, 21). This profound loss of immune function manifests such that patients with advanced HIV (e.g., CD4 cell counts <100 cells/mm³) often present with atypical forms of the disease that have disseminated beyond the lung (21). Clinically, these forms of TB are more likely to be sputum smear negative (if pulmonary) and are difficult to diagnose, particularly in resource-limited settings (22).

Although a comprehensive understanding of immunologic control of *M. tuberculosis* is lacking, CD4 cells are considered essential for adaptive immune function to the pathogen in humans (23). IFN γ -secreting peripheral blood mononuclear cells (PBMCs) and tumor necrosis factor- α (TNF α) appear particularly important, given insights gained from the inability to control mycobacterial infections in some patients with IFN γ receptor polymorphisms and the increased risk of reactivation TB seen in patients with autoimmune diseases treated with TNF α receptor antagonists (24, 25). Impairment of cellular immune function directed at *M. tuberculosis* has been associated with greater bacillary burden and worse treatment outcomes in pulmonary TB (26, 27) and may explain, at least in part, the predilection for disseminated TB in patients with advanced HIV. Furthermore, lack of specific cellular immune responses to *M. tuberculosis* were shown by Whalen et al to be a strong determinant of death in patients with HIV/TB in Uganda (28).

Despite this early and clinically relevant immunologic loss, however, several studies have indicated that adaptive immune function needed for control of *M. tuberculosis* can be recovered to a considerable degree on ART. Furthermore, the degree to which this occurs appears to be highly heterogeneous. Indeed, pathogen-specific immune function, measured in peripheral blood, can rapidly increase several-fold after ART initiation in both early and advanced HIV, but some patients fail to recover such function despite virologic suppression (5, 29, 30, 31). Epidemiologically, the risk of TB decreases substantially as CD4 cell counts increase on ART over time, yet HIV-infected patients generally remain at increased risk of TB even when CD4 cell counts exceed 350 cells/mm³ (3, 32). Given that some patients with advanced HIV/TB rapidly recover pathogen-specific immune function on ART while others do not, it is possible that better microbiologic control afforded by a rapidly recovering cellular immune system is associated with improved probability of survival on ART. However, patients with advanced HIV/TB are at increased risk for both early mortality and TB-IRIS (5, 14), and to the extent that these outcomes are, respectively, associated with

failed and rapid recovery of cellular immune function, interventions that alter immune recovery to decrease risk of one outcome could increase the risk of the other. To date, studies relating immune recovery to outcomes in HIV/TB have focused primarily on TB-IRIS, whereas treatment strategy trials have focused largely on evaluating timing of ART initiation after TB diagnosis. However, as discussed below, persistently high mortality rates among patients initiated on both anti-tubercular therapy and appropriately timed ART indicate that further studies clarifying mechanisms of clinical demise in these patients are urgently needed.

Substantial mortality despite TB treatment and timely ART initiation persists in advanced HIV/TB

Recent data from multiple clinical trials evaluating timing of ART in HIV/TB have demonstrated that early initiation of ART in co-infected individuals with advanced HIV is superior to delayed ART following anti-tubercular therapy initiation. The CAMELIA trial in Cambodia compared mortality rates among 661 patients with TB and very advanced HIV (median CD4 cell count of 25 cells/mm³) randomly assigned to either earlier (2 weeks after beginning tuberculosis treatment) or later ART initiation (8 weeks after) (7). In this study, the risk of death was significantly lower in the group that received ART earlier, with 59 deaths among 332 patients (18%), as compared with 90 deaths among 329 patients (27%) in the later-ART group (hazard ratio, 0.62; 95% confidence interval [CI]; 0.44 to 0.86; P=0.006). In AIDS Clinical Trials Group Study 5221 (the STRIDE study), a multi-site international clinical trial that also evaluated early versus delayed ART initiation in HIV/TB and where the median baseline CD4 count was somewhat higher than in CAMELIA (77 cells/mm³), the effects of early ART on outcomes were mainly in patients with baseline CD4 counts <50 cells/mm³ (16% of these patients died or had a new AIDS-defining illness in the earlier ART group versus 27% in the delayed ART group) (6). Similar results, demonstrating improved survival with ART initiated before versus after 4 weeks of TB treatment only in those with low baseline CD4 counts, were also reported from another large trial in South Africa (incidence-rate ratio, 0.32; 95% CI, 0.07 to 1.13; P=0.06) (8). Thus, all three of these trials indicate that the most advanced patients have an especially urgent need for rapid recovery of immune function.

While these studies demonstrated that early ART improves survival in those with advanced HIV/TB, a strategy now explicitly advocated by WHO (33), they did not clarify the mechanisms of death in patients who died despite initiating both ART and TB treatment. Indeed, a striking and under appreciated finding of these studies was the substantial number of patients who died despite initiation of both ART and TB treatment. For example, in STRIDE, 55 of 783 patients (7%) with HIV/TB who began ART and anti-tubercular therapy died during 48 weeks of follow-up (6). In CAMELIA, where baseline CD4 counts were considerably lower, mortality despite ART and TB treatment initiation was even higher: 120 of 661 (18%) patients died despite initiation of both treatments (7). Thus, a key gap limiting further improvements in outcomes is the need to better understand the mechanisms responsible for this unacceptably high early mortality despite therapy. While rare cases of life-threatening or fatal medication toxicity occur (34), available data strongly suggest that

the magnitude and characteristics of immune recovery on ART are the critical determinants of treatment outcomes in advanced HIV/TB.

From this perspective, it is useful to consider two simplified, broad phenotypes of pathologic immune recovery on ART in HIV/TB: inflammatory, leading to TB-IRIS; and ineffective, leading to failure to control TB or non-TB infections and death. While the immunopathology of these two broad phenotypes is incompletely understood, both should be considered while designing interventions aiming to improve treatment outcomes on ART in HIV/TB. As previously mentioned, TB-IRIS has been the subject of multiple reviews and investigations (14, 16, 35), whereas “immune failure” has received comparatively little attention.

Overwhelming infections, death on TB treatment, and variable immune recovery after ART in advanced HIV/TB

Studies published prior to the HIV epidemic demonstrated that patients with TB may die despite control of their infection if they have experienced extensive tissue destruction (36, 37). However, in autopsy studies of patients with HIV/TB, even in those on treatment, death is more often due to overwhelming TB. An autopsy study among predominantly HIV-infected, ART-naïve patients from Botswana, for example, demonstrated that 90% of those with a diagnosis of pulmonary TB had post-mortem evidence of disseminated infection, even though nearly all had been started on standard anti-tubercular therapy (38). Wong et al reported a needle-based autopsy study in South Africa of 39 patients with a median CD4 count of 50 cells/mm³, 25 of whom were on ART (39). Nineteen of 25 (76%) had mycobacterial infection identified as the primary cause of death (1 due to *M. avium*, all others due to *M. tuberculosis*), all had evidence of infection that had disseminated beyond the lung, and over half of those who died on ART due to disseminated TB were on anti-tubercular therapy. While TB in these patients may have caused extensive tissue destruction prior to starting treatment, these data, along with studies documenting the inability to control mycobacterial infection despite treatment in patients with polymorphisms of the IFN γ receptor (24), demonstrate that anti-tubercular therapy can be insufficient to control the disease in some patients with profound cellular immunosuppression.

Furthermore, other pathogens also contribute to the high mortality despite appropriate TB and ART treatment in patients with advanced HIV/TB. Autopsy studies indicate that patients with HIV/TB often demonstrate tissue evidence of invasive bacterial, viral, or fungal infections, including *Pneumocystis jirovecii*, *Isospora belli*, *Salmonella* spp., *Toxoplasma gondii*, *Streptococcus pneumoniae* and CMV (40, 41). The finding that cotrimoxazole, in addition to TB treatment, decreases death or hospitalization in patients with HIV/TB regardless of the CD4 count also implicates non-TB co-pathogens in morbidity and mortality in these individuals (42–44).

The risk of TB dissemination and overwhelming infections clearly increases as CD4 cell counts decline (21), and the longer-term immune recovery associated with ART clearly helps patients with HIV avoid future opportunistic illnesses (45). However, among patients who initiate ART during TB treatment, does the magnitude of immune recovery on ART

influence near-term survival? The number of cells responding specifically to *M. tuberculosis*, which have been directly linked to the quantitative burden of the pathogen in sputum (26) and to outcomes in TB treatment (27), can rapidly increase within days after ART initiation, before many early deaths in HIV (and by extension, advanced HIV/TB) occur (5, 30, 46). Patients with advanced HIV/TB who recover immune function rapidly may be able to control TB disease, with successful outcomes, whereas those in whom profound immunosuppression persists may suffer from disease dissemination despite therapy, and a resultant high risk of death. This concept is also generally supported by numerous epidemiologic studies demonstrating that poorer CD4 cell response to ART in those who virologically suppress is associated with an increased risk of AIDS progression and death in general, although these studies have focused on longer term responses and were not conducted specifically in patients with HIV/TB, where TB-IRIS is a particular concern (45). However, data linking immune recovery and early clinical outcomes in patients with HIV/TB are scarce.

When anti-tubercular therapy and ART aren't enough: Immunological "failure" and early mortality in advanced HIV/TB

Data from a prospective study enrolling patients with advanced HIV (pre-ART CD4 count < 125 cells/mm³) and pulmonary TB in Botswana demonstrated that patients who died in the initial 6 months after ART initiation had significantly poorer CD4 cell count recovery 4 weeks after ART initiation (median 8 (IQR -8 to 43) versus 61 (IQR 24 to 131) cells/mm³, $P < 0.001$) (5). This association between poor early immunological response and death was seen despite a similar degree of baseline immunosuppression in those who died and survived, and despite nearly identical rates of early virologic response (median drop in HIV-1 RNA levels of 3.1 vs 3.0 log₁₀ copies/mL, respectively). Furthermore, each 20-cell increase in CD4 cell response from baseline to week 4 of ART was associated with a 40% decrease in the odds of death within 6 months (odds ratio 0.59 (95% CI, 0.41–0.87), and this effect was independent of age, sex, other opportunistic illnesses. Patients with HIV/TB who died also had poorer recovery of PBMC IFN γ secretion in response to purified protein derivative (PPD), as measured by ELISPOT. Moreover, while 22% of patients in the study developed paradoxical TB-IRIS, only 1 patient who died developed the syndrome as conventionally defined (discussed further, below) (16).

These findings raise the next question, namely what is the specific mechanism responsible for death in those who fail to achieve rapid pathogen-specific immune function. Logically, fatal failure to recover pathogen-specific immune function should be linked to death due to that specific pathogen. While the study from Botswana demonstrating an association between death and poor immunological response did not have clinical or autopsy confirmation that death was due to uncontrolled disseminated TB (5), the link between antigen-specific immune function and microbiologic control of *M. tuberculosis* (26, 27) combined with overwhelming TB as a common cause of death in patients with advanced untreated HIV/TB (39, 40), suggest that uncontrolled TB as a contributing cause of death in these patients is highly likely. Thus, in this study, failure to achieve rapid immunological recovery, and not excessive immune response, was the main predictor of death. These data

indicate that, in patients with advanced HIV/TB, “immunological failure” on ART may need to be addressed by enhancing relevant immune recovery in order to further improve survival.

TB-IRIS and advanced HIV/TB

It is possible, however, that interventions that enhance immune function beyond that associated with ART initiation could be detrimental to HIV/TB survivors, if doing so leads to an increased risk or increased severity of TB-IRIS. Several recent reviews have focused on the pathophysiology of TB-IRIS (13, 16, 47). Briefly, IRIS can be either “paradoxical” or “unmasking” in mechanism. Paradoxical IRIS is worsening of TB (or other OI) disease symptoms after ART initiation in a patient with a known TB or OI diagnosis at the time of ART initiation, whereas unmasking IRIS is the clinical appearance of previously unrecognized TB or other OI after ART initiation (16). Multiple studies have shown that a consistent risk factor for TB-IRIS is more advanced HIV disease stage at ART initiation (9–12, 48). Another risk factor for TB-IRIS is initiating ART closer to the time of TB treatment initiation, which may be related to ART initiation during a period of greater antigen “load” (10–12). Immunologically, development of TB-IRIS has been associated with the rapid expansion of pathogen-specific CD4 cells following ART initiation (30, 49). Not all studies have found this relationship, however (50), and the causal role of the rapid recovery of these cells in the pathophysiology of TB-IRIS is uncertain (47). More recently, studies have focused on a possible role of the innate immune system and natural killer (NK) cells (51, 52), or the possibility that macrophages may be “primed” with a very high burden of infection during immunosuppression, which results in an exaggerated immune response when CD4 cells are recovered on ART (47). While intriguing data are emerging, precise mechanisms of TB-IRIS remain incompletely defined.

While severe forms of TB-IRIS occur, meta-analyses have shown that death due to TB-IRIS is rare (<5% of TB-IRIS cases are fatal) (17). However, data from trials evaluating timing of ART initiation in HIV/TB have recently shown that earlier initiation of ART is associated with an increased risk, and severity of TB-IRIS. For example, in the South African trial of timing of ART in HIV/TB (10), patients who began ART within 4 weeks after TB treatment initiation had an incidence of TB-IRIS that was more than twice that seen in those initiating ART later. Patients initiating ART early after TB diagnosis in this trial also had a significantly increased risk of TB-IRIS-related hospitalization (10). An increased risk of TB-IRIS in patients initiating ART early was also seen in the STRIDE and CAMELIA studies (11, 12). Given new WHO guidelines recommending earlier ART initiation in patients with advanced HIV/TB, it is therefore likely that TB-IRIS, and severe TB-IRIS, will be increasingly common.

Even though it is rarely fatal, the prominent inflammation and morbidity seen clinically in some patients with more severe forms of TB-IRIS has led to randomized clinical trials evaluating use of immunomodulatory agents as TB-IRIS prevention strategies, including corticosteroids, non-steroidal anti-inflammatory agents, and the CCR5 inhibitor maraviroc, beginning at the time of ART initiation. Theoretically, anti-inflammatory therapy could blunt the rapid increases in inflammation associated with TB-IRIS development. Corticosteroids have previously been shown to safely improve symptomatic recovery in patients who had

developed TB-IRIS (53) and have been associated with a decrease risk of death in patients with all forms of TB in a recent systematic review and meta-analysis (54). However, use of immunosuppressive agents in patients with the highest risk of TB-IRIS, namely, those with advanced HIV/TB, carries a risk of further immunosuppression.

Improving safe and effective immune recovery in advanced HIV/TB: To inhibit or enhance?

Patients with advanced HIV/TB are thus at substantial increased risk of both immunological failure and TB-IRIS, suggesting that adjunct immunotherapies may improve outcomes in this patient group. Until now, the purposes of immunotherapy in TB have generally been considered 1) to enhance treatment of multi-drug (MDR-TB) and extensively drug-resistant TB (XDR-TB) for which antibacterial drugs are sub-optimally effective, 2) to shorten the duration for drug-sensitive TB, 3) to reduce TB recurrence and 4) to alleviate immunopathological damage (55). While a review of immunotherapy in TB is beyond the scope of this paper, and several excellent reviews have been published recently (55, 56), the dominant problem of early mortality after ART initiation indicates that immunotherapy should be investigated in advanced HIV/TB. Ideally, such therapy in would rapidly increase pathogen-specific immune function (to decrease mortality risk and aid in pathogen clearance) while simultaneously decreasing (or at least not enhancing) harmful inflammation. However, the optimal approach, let alone the specific agents to be used, as immunotherapy in these patients are unclear. Most specifically, should immunotherapy in advanced HIV/TB focus primarily on inhibiting inflammation (to decrease risk of TB-IRIS) or enhancing functional immune recovery on ART (to decrease risk of early mortality)?

Augmenting pathogen-specific immunity versus minimizing risk of TB-IRIS: Necessarily in conflict?

While a focus on immunosuppression after ART initiation could increase risk of death due to inadequate pathogen control, and immune enhancement to augment pathogen control could lead to severe TB-IRIS, alternative hypotheses also are plausible, where the former improves immune recovery and the latter decreases pathological inflammation, as shown in Figure 1. For example, prednisone use for treatment of TB-IRIS in a randomized trial was associated with a decrease in IL-6 and other inflammatory cytokines, but not with a decrease in the number of pathogen-specific PBMCs (57). One possible explanation for this could be that corticosteroids decrease high levels of generalized immune activation, commonly seen in HIV/TB, which are associated with impaired T cell redistribution from lymph nodes and immune recovery on ART (58, 59). In this scenario, it is possible that corticosteroids could paradoxically enhance CD4 cell and pathogen-specific immune recovery in patients with advanced HIV/TB by decreasing immune activation. If this is true, corticosteroids initiated at the time of ART in advanced HIV/TB may not only reduce TB-IRIS incidence and severity but could conceivably also improve survival (Figure 1). Consistent with this notion, the Botswana study evaluating early mortality demonstrated that patients who had poor immunologic recovery and died also had significantly higher levels of IL-6 and C-reactive protein (CRP) after 4 weeks on ART compared to those who survived (5). Higher

pretreatment levels of immune activation (e.g., IL-6) have also been associated with mortality on ART in patients without TB in numerous other settings (60, 61). High levels of immune activation is associated with sequestration of T cells in lymph nodes, lymph node fibrosis, damage of lymph node architecture required for access to and production of the T cell survival factor IL-7, and impaired T cell reconstitution on ART (58, 62). If poor immune recovery in these individuals was in part caused by excessive immune activation, as previous studies in patients without TB have shown (59, 63), administration of anti-inflammatory agents to these patients could potentially enhance CD4 T cell and pathogen-specific immune recovery. Studies in animal models of TB recently have demonstrated improved rates of bacillary clearance and reduced pathology afforded by compounds that reduce TNF α levels (such as phosphodiesterase inhibitors) (64–66). Furthermore, inhibition of inflammation may improve access of drugs to *M. tuberculosis* (67), and high-dose corticosteroids hastened improved sputum clearance in patients with HIV/TB in one randomized clinical trial (68).

Conversely, immune enhancement, perhaps by cytokine therapy, is an alternative approach that has been tested in patients with TB and holds promise in HIV/TB (55, 56, 69). For example, IL-7 promotes T cell development and function via the IL-7 receptor, which is expressed by naïve and central memory T cells (70). IL-7 increases the number of circulating CD4 cells, improves cellular immune function, decreases regulatory T cells in circulation and increases the diversity of the T cell receptor (TCR) repertoire, which may be particularly important if this translates into improved control of not just TB but the myriad types of co-pathogens found in advanced HIV/TB (71, 72). Importantly, IL-7 has also been shown to be safe and well tolerated in patients with HIV, and led to increased CD4 T cell numbers and other potential immunological benefits (71, 72). Although the functional capacity of these cells in terms of controlling *M. tuberculosis* has not been defined, relatively short courses of IL-7 substantially increase both naïve and effector memory CD4 cell recovery on ART (72). Furthermore, unlike IL-2, cells stimulated by IL-7 appear to negatively modulate suppressive T regulatory cells (73). The marked failure to recover CD4 cell numbers and PPD-specific immune responses in those who suffered early mortality despite suppressive ART in the Botswana study suggests that the most pressing need of these advanced patients is rapid T cell recovery (5). This approach therefore holds promise for improving survival in patients with advanced HIV/TB.

However, cytokine therapy could theoretically increase harmful inflammation if massive restoration of T cell numbers drive pathologically high levels of inflammation. Multiple studies have demonstrated rapid increases in pro-inflammatory cytokines in patients developing TB-IRIS, and immune enhancement with interventions other than ART could therefore be detrimental (74–77). On the other hand, it is equally plausible that IL-7 or other cytokine therapy could decrease TB-IRIS risk if this risk is driven primarily by antigen load during ART, as suggested by data linking IRIS risk with a shorter interval between TB treatment and ART initiation (10, 12). Specifically, if IL-7 administration resulted in more rapid pathogen clearance, that effect could paradoxically decrease inflammation and TB-IRIS risk (Figure 1). Consistent with this, more rapid pathogen clearance from the cerebrospinal fluid has been safely achieved by administration of IFN γ to profoundly immunosuppressed patients with HIV and cryptococcal meningitis (78). In TB, a trial of adjunctive IFN γ administration in a group composed primarily of HIV-uninfected adults

resulted in rapid increases in pathogen-specific PBMCs, more rapid resolution of symptoms, and an increased probability of sputum smear conversion at 4 weeks (69). Recombinant human IL-2 has also been investigated in patients with pulmonary TB, but did not show benefit (79). However, data on the effects of immunotherapy in patients with HIV/TB are presently scarce, and further study in patients with advanced disease is needed. The efficacy of immunotherapy on HIV/TB disease outcomes is likely to be modified by HIV disease stage, as was seen in the variability of the effect of early ART administration on outcomes in trials evaluating early versus delayed ART (6, 8). Another issue that would need to be overcome is relationship of administration relative to ART initiation.

Importantly, emerging data suggest that factors associated with an increased risk of TB-IRIS might (conceptually at least) be similar to those linked to immunological failure and death in HIV/TB, in that both are likely driven by the burden of the infection (and antigen) at the time of ART initiation. Thus, while immune responses underlying TB-IRIS and early mortality appear different on the surface, interventions that decrease pathogen burden more rapidly may move patients away from each end of the pathologic spectrum. Immune recovery and inflammation could improve and decrease, respectively, as pathogens are more rapidly cleared.

Conclusion

Patients with advanced HIV/TB suffer from high rates of morbidity and mortality despite initiation of both ART and TB treatment. Simultaneously at risk for both inadequate immune recovery and death, and pathologic inflammation and TB-IRIS, patients with advanced HIV/TB will likely benefit from interventions that can promote immune recovery that controls pathogens with a minimal degree of damage to the host. Further study of these agents specifically in this high-risk group should be pursued to improve treatment outcomes in HIV/TB.

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Figure 1. Advanced HIV/TB Coinfection: Negative outcomes, postulated pathogenic mechanisms, and potential interventions

Factors driving negative outcomes are shown in blue, negative outcomes in yellow, and potential beneficial interventions in pink. High TB antigen and/or pathogen burden leads to high levels of immune activation. High levels of immune activation may promote either poor cellular immune recovery and early mortality (left) or exuberant inflammation and TB-IRIS (right) after ART initiation. Augmentation of specific immune function (A, in pink) may ameliorate early mortality by improving immune recovery and pathogen control (thick pink arrow, left). While the theoretical risk of increased inflammation and IRIS exists, it is also plausible that better early control of the high antigenic burden, as has been shown in Cryptococcal meningitis, may decrease inflammation and risk of TB-IRIS (thin pink arrow, from left). Conversely, anti-inflammatory therapy (B, in pink) may reduce the exuberant inflammation associated with TB-IRIS (thick pink arrow, right). While the potential to inhibit immune recovery exists, reduction of nonspecific inflammation may enable better recovery of specific immune function, without negative effects or even beneficial effects on early mortality (thin pink arrow, from right).