



Tuberculosis and HIV Coinfection

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Tuberculosis (TB) and human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) constitute the main burden of infectious disease in resource-limited countries. In the individual host, the two pathogens, *Mycobacterium tuberculosis* and HIV, potentiate one another, accelerating the deterioration of immunological functions. In high-burden settings, HIV coinfection is the most important risk factor for developing active TB, which increases the susceptibility to primary infection or reinfection and also the risk of TB reactivation for patients with latent TB. *M. tuberculosis* infection also has a negative impact on the immune response to HIV, accelerating the progression from HIV infection to AIDS. The clinical management of HIV-associated TB includes the integration of effective anti-TB treatment, use of concurrent antiretroviral therapy (ART), prevention of HIV-related comorbidities, management of drug cytotoxicity, and prevention/treatment of immune reconstitution inflammatory syndrome (IRIS).

Tuberculosis and HIV/AIDS (acquired immunodeficiency syndrome) constitute the main burden of infectious disease in resource-limited countries. In the individual host, the two pathogens, *Mycobacterium tuberculosis* and HIV, potentiate each other, accelerating the deterioration of immunological functions and resulting in premature death if untreated.

EPIDEMIOLOGY OF HIV AND HIV-TB

The Global Burden of HIV Infection

At the end of 2012, an estimated 34.5 million adults and children worldwide were living with

HIV (WHO 2013). There were 2.3 (1.9–2.7) million estimated new HIV infections globally the same year, showing a 33% decline in the number of new infections from 3.4 (3.1–3.7) million in 2001. At the same time, the estimated number of AIDS deaths was also declining with 1.6 (1.4–1.9) million AIDS deaths in 2012, down from 2.3 (2.1–2.6) million in 2005, in part because of the increasing number of people receiving antiretroviral therapy. The HIV/AIDS epidemic affects all parts of the world, but the global burden of infection with HIV is highest in developing countries, among which the sub-Saharan Africa remains most severely affected. It is esti-

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Editors: Stefan H.E. Kaufmann, Eric J. Rubin, and Alimuddin Zumla

Additional Perspectives on Tuberculosis available at www.perspectivesinmedicine.org

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Cite this article as *Cold Spring Harb Perspect Med* 2015;5:a017871

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mated that nearly 5% (1 in every 20) of adults in sub-Saharan Africa live with HIV and account for 69% of the people living with HIV worldwide (UNAIDS 2012). Whereas the great proportion of HIV infection is attributable to HIV-1, HIV-2 is responsible for limited epidemics in specific countries in West Africa, such as Cape Verde, Guinea-Bissau, Gambia, Ivory Coast, and Senegal, and is also present in European countries with historical long connections with these African countries like Portugal and France (Camacho 2012).

The Epidemiology of Dual TB-HIV Infection

Some 14 million individuals worldwide are estimated to be dually infected with HIV and *M. tuberculosis* (Getahun et al. 2010), and TB remains the leading cause of death among people living with HIV. HIV infection is estimated to increase the risk of TB 20-fold compared with HIV-seronegative individuals in high HIV-prevalence countries (WHO 2013).

Of the estimated 8.7 million people who developed TB globally in 2012, 1.1 million (13%) were estimated to be HIV-coinfected. Of the 2.8 million people with TB who actually were screened for HIV in 2012, 20% tested HIV-positive, including 42% of people with TB in sub-Saharan Africa. More than 75% of the estimated HIV-positive incident TB cases live in just 10 countries (Ethiopia, India, Kenya, Mozambique, Nigeria, South Africa, United Republic of Tanzania, Uganda, Zambia, and Zimbabwe) (WHO 2013).

In sub-Saharan Africa, the age-distribution in the population is strongly skewed toward the younger age groups, and more than half of the population aged 15–49 yr are estimated to be infected with *M. tuberculosis* and also develop active TB more frequently (Styblo 1989; Nunn et al. 1994). These young adults are also at greatest risk for HIV infection, thus resulting in overlapping epidemics in this age range (Girardi et al. 2000; Martinson et al. 2011a).

The increased incidence of active TB in HIV-infected individuals can be attributed to at least two mechanisms: the increased reactivation of latent TB or increased susceptibility to *M. tuber-*

culosis infection. The increased risk of active TB among HIV-infected persons was initially mainly attributed to an increased risk of reactivation of a latent infection (Selwyn et al. 1989; Girardi et al. 2000); however, a growing body of evidence suggests that both situations are present and should be carefully analyzed for different countries/populations. Studies performed in urban settings in the United States indicated that almost two-thirds of *M. tuberculosis* isolates from HIV-infected patients appeared in clusters, suggesting increased recent infections (Small et al. 1994; Allwood et al. 1997). Further support for this suggestion was provided by DNA fingerprinting of nosocomial TB outbreaks, including transmission of multidrug-resistant (MDR) strains (Beck-Sague et al. 1992; Daley et al. 1992; Edlin et al. 1992; Coronado et al. 1993). These studies showed rapid progression to symptomatic disease in immunosuppressed HIV-infected individuals after de novo infection. In India, a TB-endemic country, most recurrences after successful treatment of TB are attributable to exogenous reinfection in HIV-infected persons but endogenous reactivation in HIV-uninfected persons (Narayanan et al. 2010). In a study of a general population cohort from Malawi, HIV infection increased the rate of recurrent TB by increasing the rate of diseases due to reinfection and not to relapse (Crampin et al. 2010), and in HIV-infected South African gold miners, recurrences were more often caused by reinfection (69%) than relapse (Charalambous et al. 2008). A recent review of epidemiological TB studies using molecular fingerprinting showed that HIV status was linked to *M. tuberculosis* clustering, suggesting that recent *M. tuberculosis* infection is the main cause of TB disease rather than reactivation of latent TB in areas endemic for TB and HIV (Houben et al. 2011). In line with early reports from nosocomial spread of MDR-TB, exogenous reinfection has been identified as an important mechanism for the development of MDR and extensively drug-resistant (XDR) TB in HIV patients in Tugela Ferry, KwaZulu Natal, South Africa (Andrews et al. 2008). Thus, both increased risk of reactivation of latent TB and increased susceptibility to de novo TB infection or reinfection are

factors to be taken into consideration in the strategies for prevention and treatment of TB including MDR- and XDR-TB in HIV-TB-endemic settings (Cohn and O'Brien 1998; Kato-Maeda and Small 2000).

INCREASED SUSCEPTIBILITY OF HIV PATIENTS TO DEVELOP ACTIVE TB

As described in the literature, the great majority of individuals infected with *M. tuberculosis* do not develop active TB. This scenario is distinct for individuals who are coinfecting with HIV (Pawlowski et al. 2012). In high-burden settings, HIV coinfection is the most important risk factor to develop active TB, which dramatically increases the susceptibility to primary infection or reinfection and also the risk of TB reactivation for patients with latent *M. tuberculosis* infection (Kwan and Ernst 2011). The main feature of immunosuppression in AIDS patients is the manifest loss of CD4⁺ T cells, in the blood, lymphoid tissues, and mucosa, which is obviously an important contributor to the increased risk of developing active TB (Moir et al. 2011). However, susceptibility to TB increases soon after HIV infection, far before the decrease of the CD4⁺ T-cell counts below 500 cells/ μ L (Sonnenberg et al. 2005), clearly showing that the mechanisms underlying the increased susceptibility of HIV-infected individuals to active TB goes beyond the CD4⁺ T-cell drop. In fact, the World Health Organization (WHO) recommends the initiation of antiretroviral therapy for any HIV-infected individual who develops TB, regardless of the CD4⁺ T-cell counts (WHO 2013). However, the modifications induced in the immune system by HIV infection that underlie the recognized increased susceptibility to TB are far from being understood.

Besides the inability to eradicate the virus from the infected host, a strong and sustained immune response against HIV is established on infection (Sauce et al. 2013). Innate and acquired components of the immune system become activated and fight viral infection. In the context of the acquired immune response, both HIV-specific B and T lymphocytes, and among these, both CD4⁺ and CD8⁺ T cells, become

activated. HIV-2 infection also causes the activation of both B and T lymphocytes, although at a much slower pace, and as a consequence also causes a slower loss of CD4⁺ T cells and progression to AIDS (Sousa et al. 2002). The activation of the T-cell population is such an important component of the HIV infection that it is recognized as a hallmark of pathogenic HIV infection. In fact, the level of immune activation is considered the best predictor of progression from HIV infection to AIDS and even to death, independently of HIV viral load (Sousa et al. 2002; Deeks et al. 2004).

Although the hallmark of the HIV infection is the loss of CD4⁺ T cells, different cell populations are preferentially deleted at distinct periods of the HIV infection. During the initial period, the effector memory CD4⁺ T cells in the gut mucosa are preferentially depleted (Mehandru et al. 2004; Brenchley and Douek 2008; Moir et al. 2011), followed by the progressive generalized loss of naïve T cells. The CD4⁺ T cells are initially reconstituted through the production of new T cells by the thymus, the increased homeostatic proliferation of the peripheral naïve T cells, and the extension of the half-life of the CD4⁺ T cells (Corbeau and Reynes 2011). However, the pool of peripheral naïve T cells tends to become progressively exhausted, and thymic production of new naïve T cells also becomes impaired as the infection progresses (Moir et al. 2011). Factors such as direct death of thymocytes, depletion of T-cell precursors within the bone marrow, and disruption of the thymic epithelia have been proposed to explain thymic failure (Ho Tsong Fang et al. 2008). In addition to the loss of T cells, the continuous stimulation renders T cells dysfunctional (Moir et al. 2011), and the desired balance between distinct T-cell populations, necessary to maintain the immune system's homeostasis, such as the proportion between naïve/effector/activated, Th17/regulatory T cells (Treg), is progressively lost (Kanwar et al. 2010; Hartigan-O'Connor et al. 2011).

Activation of the immune system in chronically HIV-infected individuals is also characterized by the increased expression of several proinflammatory cytokines and other biomark-

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ers associated with the activation of the immune system (Neaton et al. 2010; Nixon and Landay 2010). Several studies have been performed attempting to correlate the expression of some of these markers with progression to AIDS, development of opportunistic diseases, and ultimately death (Neaton et al. 2010; Nixon and Landay 2010).

Distinct mechanisms have been proposed to explain the sustained immune activation in HIV-infected individuals. One of the most studied hypotheses is the translocation of bacterial products from the gut to the blood stream. However, to which extent this is necessary and the contribution of the mature T-cell depletion from the gut mucosa are controversial (Douek 2007; Vassallo et al. 2012). It has also been suggested that sustained immune activation, even in virus-suppressed individuals, is caused by continuous replications of HIV (Allavena et al. 2013). The excessive production of type-1 interferon (IFN) by hyperresponsive plasmacytoid dendritic cells during the primary infection, and the following chronic activation of these cells, may contribute to the general immune activation (Fitzgerald-Bocarsly and Jacobs 2010). Some authors have also suggested that a dysregulation of Treg cells would be responsible for the sustained immune activation in HIV-infected individuals (Chevalier and Weiss 2013).

An important question addressed in the most recent years is—What are the alterations of the immune system induced by the HIV infection that precede and are potentially maintained during CD4⁺ T-cell depletion that renders the HIV-infected individuals so susceptible to develop active TB? Although general alterations of the immune system have been proposed, some authors have added the possibility that HIV infection perturbs specifically the *M. tuberculosis*-specific T cells. In fact, a selective depletion of *M. tuberculosis* antigen-specific CD4⁺ T cells was shown to occur before generalized CD4⁺ T-cell depletion in HIV-infected individuals (Geldmacher et al. 2008, 2010). This increased depletion of the *M. tuberculosis*-specific CD4⁺ T cells has been associated with increased susceptibility to productive HIV-1 infection of cells producing interleukin-2 (IL-2).

An increasing body of evidence suggests that cells expressing a specific set of cytokines simultaneously, referred to as polyfunctional T cells (expressing INF- γ , IL-2, tumor necrosis factor [TNF], and/or IL-17), are essential for a protective immune response to *M. tuberculosis*. In accordance, one study comparing the number of these cells in the lung of TB individuals showed that they are present in quite reduced numbers in HIV-coinfected patients (Kalsdorf et al. 2009).

CD8⁺ T cells have been shown to play a relevant role for the control of latent TB (Behar 2013; Nunes-Alves et al. 2014). Disrupted CD8⁺ T-cell function in HIV-infected individuals might occur because of direct dysfunction of these cells or because of the abrogated activity of the CD4⁺ T cells in general and/or the specific loss of *M. tuberculosis*-specific CD4⁺ T cells (Haas et al. 2011).

An increased production of TNF has been suggested to cause increased susceptibility to active TB (Roca and Ramakrishnan 2013). This has been shown in the context of individuals that naturally produce increased levels of TNF in response to *M. tuberculosis* infection (Roca and Ramakrishnan 2013). HIV infection has been shown to impair TNF-mediated macrophage apoptosis upon infection with *M. tuberculosis* (Patel et al. 2007). Decreased apoptosis and increased necrosis of infected macrophages have been shown to assist infection and to delay the establishment of antigen-specific immune responses (Behar et al. 2010). In accordance, it is reasonable to consider that the general activation of the immune system, characteristic of HIV infection, renders the hosts more susceptible to develop active TB.

Regarding potential alterations on the innate immune response, several studies have addressed the ability of macrophages to control the growth and/or kill intracellular *M. tuberculosis*. However, data in this respect have been quite controversial with some reports showing decreased ability of the macrophages from HIV-infected patients to control *M. tuberculosis* growth (Pathak et al. 2010), whereas others suggest no effect of HIV infection on the ability of the macrophages to control *M. tuberculosis* (Kalsdorf et al. 2009).

The IFN- γ /IL-12 axis is central for the interaction between the initially infected innate cells and the activation of antigen-specific T cells. The suppressor of cytokine signaling 1 (SOCS1) and IL-27 have been shown to impair the immune response against *M. tuberculosis* through down-regulating this axis (Carow et al. 2011; Pearl et al. 2004). T-cell exhaustion is a common alteration found in chronic HIV-infected patients. Markers of T-cell exhaustion such as programmed-death 1 (PD-1) and T-cell immunoglobulin and mucin domain 3 (Tim-3) (Day et al. 2006; Jones et al. 2008) both involved in the down-regulation of host immune responses, have been associated with chronic progressive HIV infection (Jones et al. 2008) and progression to active TB (Wang et al. 2011), indicating that similar inhibitory receptor/ligand interactions play a role in modulating host immunity to both HIV and *M. tuberculosis* infections in humans.

Other alterations of the immune system among HIV-infected individuals reported to promote *M. tuberculosis* infection and active TB are the up-regulation of *M. tuberculosis* entry receptors on macrophages (Rosas-Taraco et al. 2006), HIV manipulation of macrophage bactericidal pathways (Spear et al. 1990), deregulated chemotaxis (Wahl et al. 1989), and a tipped Th1/Th2 balance (Havlir and Barnes 1999).

IRIS

The introduction of antiretroviral therapy (ART) drastically reduced the mortality of HIV-infected patients. By effectively suppressing the replication of HIV, most patients under ART present a reduced viral load and a concomitant raise in the number of peripheral CD4⁺ T cells, especially evident during the first months of treatment (Autran et al. 1997). Unfortunately, this rapid CD4⁺ T-cell reconstitution leads, in some patients, to the phenomenon known as immune reconstitution inflammatory syndrome (IRIS) also referred to as immune restoration disease (Pearl et al. 2004). IRIS develops shortly after the initiation of ART and is associated with an exacerbated immune response to a coinfecting pathogen.

Whereas IRIS can occur because of coinfection with several pathogens, and even be associated with autoimmune diseases (French et al. 2004; Lawn et al. 2005a), it has been estimated to be because of coinfection with *M. tuberculosis* in $\sim 15.7\%$ of the cases (Lawn et al. 2005b; Muller et al. 2010). This exacerbated immune response might be presented in one of two distinct forms, defined as paradoxical IRIS, when it occurs as the result of recurrent, new, or worsening symptoms of coinfection under treatment, and referred to as unmasking IRIS when associated with a subclinical infection. Because of the lack of distinctive biomarkers or definitive diagnostic tests, the definition of IRIS in TB-HIV-coinfected patients is difficult. A consensus clinical case definition for TB-IRIS has been defined (Meintjes et al. 2008a). Studies on patients that developed TB-IRIS led to the determination of the most obvious risk factors for the development of this syndrome, although the underlying mechanisms responsible for IRIS are still not clearly defined. Low CD4⁺ T lymphocyte counts before ART initiation ($< 50\text{--}100$ cells/ μL) followed by a successful CD4⁺ T-cell raise is one of the most important risk factors to develop IRIS (Olalla et al. 2002; Breton et al. 2004; Ratnam et al. 2006; Bourgarit et al. 2009). Another important risk factor is the initiation of TB treatment shortly after initiation of ART (Navas et al. 2002; Tansuphasawadikul et al. 2007). Extrapulmonary TB has also been reported to be associated with a higher risk of TB-IRIS (Manosuthi et al. 2006; Burman et al. 2007).

It has been extremely difficult to determine the mechanisms responsible for IRIS because of the difficulty in defining and making use of all necessary control groups (Lai et al. 2013) and to a certain extent also to the lack of a satisfactory animal model. Both alterations in the acquired and the innate immune response associated with ART have been proposed as being potentially responsible for TB-IRIS. One of the most explored mechanisms has been the expansion of antigen-specific Th1 CD4⁺ T cells shortly after ART initiation. Although several studies propose these CD4⁺ T cells as a causal link for IRIS (Bourgarit et al. 2006), it is far from being

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consensual because several other studies showed similar development of Th1-CD4⁺ T-cell expansions in the absence of IRIS (Lai et al. 2013). A defect on the CD4⁺ Treg cells has been investigated as a potential mechanism responsible for the CD4⁺ T-cell exacerbated response. Because Treg cells are essential to maintain T-cell homeostasis, this hypothesis sounded obvious; however, data are contradictory (Meintjes et al. 2008b; Seddiki et al. 2009).

In addition to a potential defect directly on the T cells, it has been reported that TB-HIV-coinfected patients with IRIS had significantly lower levels of specific antibodies to the phenolic glycolipid (PGL-TB1) antigen from *M. tuberculosis*, compared with patients without TB-IRIS (Simonney et al. 2008).

Elevated production of pro- and anti-inflammatory cytokines has been consistently associated with TB-IRIS, although a casual effect has not been shown (Lim et al. 2008; Worsley et al. 2010; Tadokera et al. 2011; Skolimowska et al. 2012). Interestingly, some of the cytokines that have been implicated are produced exclusively by cells of the innate immune systems, strongly suggesting that innate immune cells play an important part in the pathogenesis of TB-IRIS (Jones et al. 2008). Among the cells of the innate immune system, it is of relevance that ART has been shown to lead to macrophage hyperactivation in response to *M. tuberculosis* antigens (Van den Bergh et al. 2006). Higher numbers of IFN- γ producing $\gamma\delta$ T cells lacking the expression of the killer immunoglobulin-related receptor (KIR⁻) were also shown (Seddiki et al. 2009). Recent studies add to the list of potential candidates the NK cells (Conradie et al. 2011) and the neutrophils (Marais et al. 2013).

TB EXACERBATES PROGRESSION FROM HIV INFECTION TO AIDS

In the HIV/*M. tuberculosis* dual interplay not only does HIV affect the progression of TB, but *M. tuberculosis* infection also has a negative impact on the immune response to HIV, accelerating the progression from HIV infection to AIDS (Pape et al. 1993; Whalen et al. 1995). Research

on the potential mechanisms underlying this effect is, however, quite scarce.

M. tuberculosis and HIV share anatomical reservoirs such as the lung (Costiniuk and Jenabian 2014), and it has been suggested that TB patients have a microenvironment that facilitates HIV infection. In fact, active TB has been associated with accelerated loss of CD4⁺ T cells and increased risk of opportunistic infections (Badri et al. 2001). The ongoing immune response against *M. tuberculosis* has been shown to increase the replication of HIV-1 in the blood (Goletti et al. 1996; Toossi et al. 2001) and at sites of *M. tuberculosis* infection in the lung (Nakata et al. 1997; Collins et al. 2002) and within activated cells including lymphocytes and CD14⁺ macrophages of the pleural space in the case of tuberculous pericarditis (Lawn et al. 2001; Matthews et al. 2012). *M. tuberculosis* induces the production of proinflammatory cytokines and chemokines, including TNF (Rosas-Taraco et al. 2006), that activate signal transduction pathways in CD4⁺ T cells and monocytic cells that also result in transcriptional activation of the long terminal repeats (LTRs) of HIV (Israel-Biet et al. 1991; Garrait et al. 1997; Hoshino et al. 2002).

In addition, in vitro experiments using *M. tuberculosis* have been shown to up-regulate HIV-1 replication in infected T cells, macrophages (Shattock et al. 1993; Zhang et al. 1995), and dendritic cells, as well as ex vivo in alveolar macrophages and lymphocytes from HIV-infected patients (Toossi et al. 1997; Goletti et al. 1998). Multiple mechanisms have been implicated, including cytokine- and chemokine-mediated mechanisms (Toossi et al. 2001; Hoshino et al. 2004), and loss of an inhibitory transcription factor CCAAT/enhancer-binding protein β (C/EBP β) (Hoshino et al. 2007). These mechanisms cause transcription activation of HIV genes, resulting in enhanced viral replication, spread to uninfected cells, and their subsequent depletion. Terminal differentiation of CD4⁺ T cells at TB disease sites leads the CD4⁺ T cells to express CCR5, an HIV coreceptor, rendering these cells more susceptible to HIV infection (Matthews et al. 2012).

Both HIV and *M. tuberculosis* infect macrophages (Landay et al. 1993; Sierra-Madero et al. 1994; Nakata et al. 1995) and trigger production of host inflammatory mediators (Kedzierska et al. 2003; Ansari et al. 2013) that subsequently regulate the immune response and disease pathogenesis. These inflammatory mediators can impose beneficial or detrimental effects on each pathogen and eventually on the host. In vitro studies have shown that *M. tuberculosis* infection can increase both HIV infection and replication within macrophages and the efficiency of virus transmission from infected macrophages to T cells (Mancino et al. 1997). Up-regulation of the coreceptors CXCR4 and CCR5 (Hoshino et al. 2004; Rosas-Taraco et al. 2006), SOCS1, which is stimulated by infection with *M. tuberculosis* (Rosas-Taraco et al. 2006), has been shown to facilitate the late replication pathways of HIV infection (Ryo et al. 2008) and mediate viral evasion of type-1 IFN antiviral signaling (Fenner et al. 2006). The transcription factors NF- κ B and NFAT5 are required for *M. tuberculosis*-induced HIV-1 replication in macrophages (Ranjbar et al. 2012).

Although the major cell targets of HIV are CD4⁺ T cells, dendritic cells have multiple roles at different stages of HIV infection (Manchez, Trends in Immunology, in press). In this context, it is suggested that *M. tuberculosis* increases HIV transinfection and induces viral sequestration within surface-accessible compartments suppressing major histocompatibility complex class II antigen processing by dendritic cells (Reuter et al. 2010) and that mycobacteria-infected bystander macrophages trigger maturation of dendritic cells and enhance their ability to mediate HIV transinfection (Mazurek et al. 2012).

Clinical Handling of TB Patients with HIV, Including IRIS

The current management of patients with HIV-associated TB includes provision of effective anti-TB treatment, use of concurrent ART, prevention of HIV-related comorbidities, management of drug cytotoxicity and prevention/treatment of IRIS (Lawn et al. 2013).

TB treatment in concomitant HIV infection follows the same principles as in non-HIV-infected individuals (for more details on TB treatment, see Sotgiu et al. 2014). However, caution is advocated because of interactions between anti-TB and -HIV drugs, such as protease inhibitors and rifamycins, in particular rifampicin. The clinical entity IRIS and the phenomenon of “unmasking TB” are now well-known complications on institution of ART in TB disease.

Drug-susceptible TB in low-incidence settings is usually treated with a 2-mo intensive phase of the four standard drugs (Sotgiu et al. 2014), followed by a 4-mo continuation phase if rifamycins and INH (isoniazid) are used. Intermittent dosing is not recommended in HIV patients during the intensive phase because it has been associated with an increased risk of treatment failure or relapse with acquired drug resistance to rifamycins (IDSA 2013) (see http://www.idsociety.org/uploadedFiles/HIVMA/Guidelines_Patient_Care/HIVMA_Standards_Practice_Guidelines/HIV_Guidelines/Guidelines_Content/adult_oi.pdf) (Nettles et al. 2004; Li et al. 2005; Swaminathan et al. 2010). During the follow-up phase, daily or a minimum of thrice weekly intermittent dosing should be used (IDSA 2013), the latter has not been associated with increased risk of relapse, treatment failures, or acquired drug resistance (Khan et al. 2010). Treatment of drug susceptible disease in coinfecting patients in high endemic settings follow the same principles as in low-endemic settings; however, the optimal duration of treatment has been debated as higher frequencies of recurrent TB has been observed in 6-mo regimens compared with 9- and 12-mo regimens (Perriens et al. 1995). However, as previously described, recurrences in standard length treatment were mainly caused by reinfection episodes (Charalambous et al. 2008; Crampin et al. 2010; Narayanan et al. 2010).

Important Interactions between Anti-TB and -HIV Drugs

Recommended first-line anti-HIV regimens are based on nonnucleoside reverse transcriptase

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inhibitors (NNRTI) with efavirenz as the drug of choice and nevirapine as an alternative (Lawn et al. 2013) (IDSA 2013). A summary of recommended anti-HIV regimens and their interactions with anti-TB drugs are shown in Table 1. As new HIV drugs are entering the market and more recently new TB drugs, updated information can be retrieved (see <http://www>

[hiv-druginteractions.org](http://www.hiv-druginteractions.org)). For cotoxicity of TB and HIV drugs see IDSA (2013).

Treatment of IRIS

In mild cases of IRIS, specific treatment is usually not necessary and both anti-HIV and anti-TB treatment should be continued (Lawn et al.

Table 1. Approaches to cotreatment for HIV-infected patients with rifampicin-susceptible tuberculosis

Combined regimes	Treatment recommendations	Drug–drug interactions
Efavirenz + rifampicin-based TB treatment	No dose adjustments TDF + 3TC/FTC + EFV (WHO-recommended optimum regimen) AZT + 3TC + EFV (alternative WHO regimen)	Rifampicin induces CYP2B6 but inhibition of CYP2A6 by isoniazid might account for increased efavirenz concentrations during TB treatment in those patients with slow CYP2B6 metabolizer genotype.
Nevirapine + rifampicin-based TB treatment	Omit 14 d lead-in phase of once daily dose of NVP TDF = 3TC/FTC = NVP (alternative WHO regimen) AZT + 3TC + NVP (alternative WHO regimen)	Rifampicin induces CYP2B6 and CYP3A4. Although TB treatment reduces nevirapine concentrations, toxicity concerns curtail increasing the dose and outcomes are acceptable (but inferior to EFV) on standard doses.
Lopinavir/ritonavir + rifampicin-based TB treatment	Double-dose lopinavir/ritonavir (800/200 mg every 12 h) or superboost lopinavir (lopinavir/ritonavir 400/400 mg every 12 h). Monitor alanine transaminase (ALT) closely.	Ritonavir counteracts this effect and adjusted doses of ritonavir or lopinavir/ritonavir are used to compensate, but lopinavir concentrations may be more variable. Increased risk of hepatotoxicity and gastrointestinal side effects.
PI/ritonavir + rifabutin-based TB treatment	Reduce rifabutin dose to 150 mg daily or thrice weekly. Monitor closely for rifabutin toxicity.	Ritonavir-boosted PIs markedly increase rifabutin concentrations and reduce its clearance necessitating reduction in the dose of rifabutin by 50% to 75%. Toxicity (neutropenia, uveitis, hepatotoxicity, rash, gastrointestinal symptoms) and suboptimal rifamycin exposures with reduced dose are concerns.
Triple nucleoside/nucleotide regime + rifampicin-based TB treatment	No dose adjustments. A triple nucleoside/nucleotide regimen should include tenofovir or abacavir. Monitor viral load.	Triple nucleoside/nucleotide regimens may perform adequately in patients with viral suppression who have not failed a first line regimen and provide alternative ART regimens in patients with contraindications to efavirenz or nevirapine, in which other options are unavailable. TB treatment has minimal effect on tenofovir concentrations. Although rifampicin induces the enzymes responsible for glucuronidation of abacavir and zidovudine, this effect is not thought to be clinically important.

Data adapted from Lawn et al. 2013.

3TC, 2',3'-dideoxy-3'-thiacytidine; ART, antiretroviral therapy; CYP, cytochrome P450; EFV, efavirenz; FTC, emtricitabine; OATP, organic anion-transporting polypeptide; NNRTI, nonnucleoside reverse transcriptase inhibitor; NVP, nevirapine; PI, protease inhibitor; TB, tuberculosis; TDF, tenofovir; WHO, World Health Organization.

2013). If symptoms are more pronounced, high-dose corticosteroids are indicated, in particular for IRIS of the central nervous system (Lawn et al. 2013; Lee et al. 2013).

STRATEGIES FOR PREVENTION OF THE LINKED EPIDEMICS OF HIV INFECTION AND TB

Treatment of HIV to Prevent TB

Focused efforts to deliver ART to all HIV-infected individuals with *M. tuberculosis* infection would reduce the number of people who develop active TB and are vital to prevent the two epidemics fueling each other. Numerous cohort studies have shown that in HIV-infected persons, ART reduces TB risk in adults (Lawn et al. 2010) as well as in children (Lawn et al. 2005a). There is recent evidence that earlier initiation of ART in HIV-infected patients with newly diagnosed TB reduces mortality significantly (Martinson et al. 2011b).

The Three Is Strategy

The WHO Three Is strategy—*Intensified* case finding, *Isoniazid* preventive therapy, and *Infection* control in clinical settings—must be effectively implemented.

Intensified Case Finding

It is recommended that people living with HIV who live with or are close contacts of active cases of TB should be prioritized for clinical evaluation of TB. Those who, after an appropriate clinical evaluation, are found not to have active TB should be treated for presumed latent TB with isoniazid preventive therapy (WHO 2013). More intensive TB screening, both for active and latent TB, with broader definitions of target populations and expanded indications for screening in high HIV prevalence settings would further improve the control of TB (Corbett and MacPherson 2013). Lack of better and adequate diagnostic methods are, however, still a barrier (Corbett and MacPherson 2013).

Isoniazid Preventive Therapy

In 2012, 42 countries provided isoniazid preventive therapy to nearly 520,000 people living with HIV. Although the trend toward increased uptake of preventive therapy is encouraging, the number of individuals currently receiving isoniazid preventive therapy is believed to represent a small fraction of the number of people living with HIV who could benefit from the intervention. Among 30 countries reporting both denominator and numerator for preventive therapy, 30% of those newly registered in care received isoniazid preventive therapy (WHO 2013, see http://www.unaids.org/en/media/unaids/contentassets/documents/epidemiology/2013/gr2013/UNAIDS_Global_Report_2013_en.pdf). Isoniazide preventive treatment has been shown to have an additive effect combined with ART on active TB prevention.

Infection Control

As discussed earlier, people living with HIV are very vulnerable to the risk of *M. tuberculosis* infection if exposed, and there is also an excess in the occupational risk of TB including MDR- and XDR-TB in sub-Saharan Africa compared with that of the general population (Kompala et al. 2013; Rothe et al. 2013). WHO recommends that TB infection control practices should be in place in all congregate settings and in health facilities providing HIV care. TB infection control practices include personal, administrative, and environmental controls as well as health worker surveillance. Informing communities and the general public about these practices will also help to reduce the spread of TB to people living with HIV (WHO 2013, see http://whqlibdoc.who.int/publications/2009/9789241598323_eng.pdf).

Vaccination

Ultimately, the most cost-effective approach to combat the two diseases would be vaccination. Presently, there is no effective vaccine, neither against TB nor HIV. Vaccination against TB and the need for and design of new TB vaccine(s) are discussed in Andersen and Kaufmann (2014).

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However, even if we have a good TB vaccine, HIV infection will most probably reduce the efficacy of this vaccine because HIV has been suggested to eliminate preferentially *M. tuberculosis*-specific T cells (Geldmacher et al. 2008, 2010).

One approach that has been suggested would be to construct a combined TB-HIV vaccine (Kaufmann and McMichael 2005), such as a recombinant BCG (Bacillus Calmette–Guérin) vaccine as a vehicle for combinations of mycobacterial and HIV antigens (Hiroi et al. 2001; Kawahara et al. 2002; Yu et al. 2007). However, the interaction of the immunomodulatory role of individual antigens of the two pathogens needs further elucidation as, for example, the major HIV antigen gp120 (Del Corral et al. 2001) and mycobacterial compounds such as glycolipids of the cell wall, particularly LAMs, PIMs, and phenolic glycolipids (Portevin et al. 2011), that play a crucial role in modulating immune responses. It is also increasingly apparent that these compounds may differ in biologic activity depending on strain lineages of the two pathogens (Locher et al. 2005; Carow et al. 2011; Portevin et al. 2011). Because both pathogens enter the host through mucosal surfaces, a combination vaccine given at mucosal sites would probably be optimal (Hiroi et al. 2001; Kawahara et al. 2002; Yu et al. 2007). However, for this end, further research in the biology of concurrent *M. tuberculosis* and HIV infections is urgently needed.

An integrated approach to the two diseases should thus lead to novel concepts and correlates of protection and to the identification of antigen targets useful for new therapies to overcome the rapidly increasing drug resistance of both diseases, as well as for vaccination (Pawlowski et al. 2012).

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Cold Spring Harb Perspect Med 2015; doi: 10.1101/cshperspect.a017871 originally published online February 26, 2015

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