LUND UNIVERSITY

Tuberculosis and HIV Co-Infection

Pawlowski, Andrzej; Jansson, Marianne; Skold, Markus; Rottenberg, Martin E.; Kallenius, Gunilla

[Link to publication]

Review

Tuberculosis and HIV Co-Infection

Andrzej Pawlowski[1][9], Marianne Jansson[2,3][9], Markus Sköld[2][9], Martin E. Rottenberg[2][9], Gunilla Källenius[1]*[9]

1 Department of Clinical Science and Education, Karolinska Institutet, Stockholm, Sweden, 2 Department of Microbiology, Tumor and Cell Biology, Karolinska Institutet, Stockholm, Sweden, 3 Department of Laboratory Medicine, Lund University, Lund, Sweden

Abstract: Tuberculosis (TB) and HIV co-infections place an immense burden on health care systems and pose particular diagnostic and therapeutic challenges. Infection with HIV is the most powerful known risk factor predisposing for *Mycobacterium tuberculosis* infection and progression to active disease, which increases the risk of latent TB reactivation 20-fold. TB is also the most common cause of AIDS-related death. Thus, *M. tuberculosis* and HIV act in synergy, accelerating the decline of immunological functions and leading to subsequent death if untreated. The mechanisms behind the breakdown of the immune defense of the co-infected individual are not well known. The aim of this review is to highlight immunological events that may accelerate the development of one of the two diseases in the presence of the co-infecting organism. We also review possible animal models for studies of the interaction of the two pathogens, and describe gaps in knowledge and needs for future studies to develop preventive measures against the two diseases.

Introduction

Tuberculosis (TB) and human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) constitute the main burden of infectious disease in resource-limited countries. Estimates by the World Health Organization (WHO) indicate that there are more than 9 million new active cases of TB and close to 2 million deaths per year [1], and that 2.6 million new cases of HIV infection and 1.8 million AIDS-related deaths occur per year [2]. *Mycobacterium tuberculosis*–HIV co-infections pose particular diagnostic and therapeutic challenges and exert immense pressure on health care systems in African and Asian countries with large populations of co-infected individuals

In the individual host the two pathogens, *M. tuberculosis* and HIV, potentiate one another, accelerating the deterioration of immunological functions and resulting in premature death if untreated. Some 14 million individuals worldwide are estimated to be dually infected [3]. TB is the largest single cause of death in the setting of AIDS [4], accounting for about 26% of AIDS-related deaths [3], 99% of which occur in developing countries [5].

Both TB and HIV have profound effects on the immune system, as they are capable of disarming the host's immune responses through mechanisms that are not fully understood. HIV co-infection is the most powerful known risk factor for progression of *M. tuberculosis* infection to active disease, increasing the risk of latent TB reactivation 20-fold [3,6]. Likewise, TB has been reported to exacerbate HIV infection [7,8]. Various lines of evidence indicate that inborn errors of immunity, as well as genetic polymorphisms, have an impact on susceptibility to TB and HIV [9].

Aspects of Immune Response to *M. tuberculosis* Infection

M. tuberculosis infects the host mainly through inhalation of aerosolized bacilli; alveolar macrophages are the primary target cells for this intracellular pathogen. Detection of *M. tuberculosis* by innate cells recognizing pathogen-associated molecular patterns, via toll-like receptors (TLRs) and nucleotide-binding oligomerization domain receptors, initiates a local inflammatory response and results in increased numbers of macrophages and dendritic cells (DCs) in infected lung tissue and draining pulmonary lymph nodes. Following activation by cytokines and innate receptor agonists, infected macrophages elicit direct bactericidal effector functions, such as reactive oxygen or nitrogen intermediates [10,11], or expression of small GTPases that can regulate endosomal trafficking [12]. DCs can phagocytose the bacteria in lung tissue, migrate to draining lymph nodes, and initiate the adaptive immune response by priming naïve T lymphocytes [13].

Cell-mediated immunity is essential for control of *M. tuberculosis* infection; activation of both CD4$^+$ and CD8$^+$ T cells is seen in active TB in humans, as well as in mice after experimental infection [14]. CD4$^+$ T lymphocytes of T helper cell type 1(Th1) are thought to be most critical [15]. Also, there is experimental evidence that CD8$^+$ T cells [16,17], as well as unconventional T cells such as CD1-restricted cells recognizing mycobacterial lipids [18], contribute to optimal control of the disease. T cells recruited to the infected lung are thought to control infection by producing interferon gamma (IFN-γ) in response to mycobacterial antigens presented by macrophages [19,20]. In turn, IFN-γ activates macrophages to kill the intracellular bacteria through reactive nitrogen and oxygen intermediates [21], and by inducing phagolysosome formation [13]. However, these mechanisms might even be present in susceptible hosts, in which the infection progresses to disease. The full knowledge of the constituents of an effective protective immune response to TB is still incomplete.

In the *M. tuberculosis*–infected host there is also a robust humoral response, with a wide spectrum of antibodies (Abs) of different

specificities and isotypes; although secondary to the cellular immune responses in terms of protection, B cells as well as certain Ab responses have been shown to be capable of playing an important role in protective immunity to TB [22].

Aspects of Immune Response to HIV Infection

HIV-1, which most commonly infects via the genital mucosa, persists as a chronic infection even though the virus elicits strong innate and adaptive, including cellular and humoral, immunity. Explanations for this may be linked to virus genomic integration and subsequent cellular latency, as well as an extreme genetic variability, which translates into constant immune escape. HIV-specific CD8$^+$ lymphocytes play a key role in the initial reduction of viremia during acute infection, but become increasingly dysfunctional and exhausted under conditions of chronic antigen persistence [23,24]. Virus-neutralizing Abs are also elicited but are frequently accompanied by immune escape, and even if some individuals develop cross-neutralizing Abs, it is debatable whether Abs play a role in the control of the virus [25].

The hallmark of HIV infection is the depletion of CD4$^+$ T cells. Interestingly, during the primary HIV infection, the cells that are preferentially depleted are the effector memory CD4$^+$ T cells in the gut mucosa [26]. These immunopathogenic features, together with the systemic and chronic state of immune activation, including accelerated T cell turnover, are thought to contribute to progression of HIV disease [27]. Thus, constant antigenic stimulation is characterized by a dysfunctional T cell population displaying loss of functional potential, i.e., cytokine production and cytotoxic activity, and proliferative ability in response to antigen stimulation. In addition, the loss of immune balance between Th17 and regulatory T cells (Treg) during HIV disease progression has recently been implicated in permeabilization of gut integrity and the pathogenesis of HIV [28].

Microbial translocation caused by gut permeability has also been suggested to contribute to systemic immune activation observed during chronic HIV infection [29]. Hyper-responsiveness of plasmacytoid DCs during the primary infection, which results in excessive type-1 IFN production and the following chronic activation of these cells, may additionally contribute to systemic immune activation and HIV-1 disease progression [30].

CD8$^+$ T cells have been implicated in the control of chronic HIV replication as suggested by studies on simian immunodeficiency virus (SIV) viremia in non-human primates after in vivo CD8$^+$ T cell depletion [31]. In addition, there are rare individuals who control HIV-1 replication to undetectable levels, i.e., elite controllers. This phenotype is strongly associated with some MHC class I alleles [32] and with the presence of HIV-specific CD8$^+$ T cells showing superior cytotoxic capacity to kill HIV-infected targets [33,34].

Programmed-Death 1 (PD-1) and T cell immunoglobulin and mucin domain 3 (Tim-3) are two examples of markers of T cell exhaustion in HIV-1$^+$ patients caused by constant antigenic stimulation [35,36]. Both molecules are involved in the down-regulation of host immune responses and play a role in maintaining T cell tolerance. A recent finding is that Tim-3 was up-regulated on virus-specific CD8$^+$ T cells in patients with chronic progressive HIV infection [36]; another recent publication reports that Tim-3 was up-regulated on antigen-specific CD8$^+$ T cells in patients with active TB [37], indicating that similar inhibitory receptor/ligand interactions play a role in modulating host immunity to both HIV and M. tuberculosis infections in humans.

TB Reactivation by HIV

It is generally thought that one-third of the world's population is latently infected with M. tuberculosis [38], although the data supporting this notion may be questioned. Also, the rate of progression from infection to disease varies greatly. Approximately 10% of M. tuberculosis–infected individuals are thought to develop overt clinical disease [6] and about half of them develop disease more than two years after infection; these cases are commonly named "reactivation" or post-primary TB [39]. Thus, the lifetime risk of developing active TB in immunocompetent adults is estimated to be 5%–10% during their lifetime, but in HIV-positive individuals this risk is increased to 5%–15% annually [40].

The depletion of CD4$^+$ T cells, which is a main feature of AIDS, is certainly an important contributor to the increased risk of reactivation of latent TB and susceptibility to new M. tuberculosis infection. There is also some evidence that CD8$^+$ T cells play a role in the control of latent TB [41–44]. Other mechanisms reported to facilitate M. tuberculosis infection and disease in individuals with HIV are up-regulation of M. tuberculosis entry receptors on macrophages [45], HIV manipulation of macrophage bactericidal pathways [46], deregulated chemotaxis [47], and a tipped Th1/Th2 balance [48]. It has also been shown that HIV impairs tumor necrosis factor (TNF)-mediated macrophage apoptotic response to M. tuberculosis and thus facilitates bacterial survival [49].

In the latent phase of TB, the bacteria are not completely eradicated despite a seemingly robust Th1 immune response. A failure or an alteration of the quality or levels of the protective adaptive immune responses or of the cross-talk with innate immune responses leads to reactivation of infection. Several immune mechanisms, such as increased levels of FoxP3$^+$ Treg cells [50], increased production of IL-27 [51], TGF-β [52,53], PGE-2 [54], SOCS1, or the decoy receptor D6 [55], or diminished levels of IFN-γ, TNF, and polyfunctional specific T cells, are believed to play a role in such reactivation. Many of these factors, such as SOCS1 or IL-27, down-regulate the IFN-γ/IL-12 axis, thereby impairing bacterial control, while others, such as the D6 decoy receptor, are mainly anti-inflammatory, but may indirectly inhibit efficient bacterial clearance. Some of these mechanisms may also underlie HIV-infected patients' increased susceptibility to active TB.

Granulomas are organized cellular structures that constitute TB's pathologic hallmark. Mycobacteria are contained within the granuloma, which, by localizing infection and thus potentially preventing spread of the disease between hosts, probably contributes to protection. CD4$^+$ T cells and TNF are important in maintaining granuloma organization. Granuloma formation may fail in individuals with a compromised immune system, and there are several hypotheses about how HIV exacerbates TB pathology through the manipulation of granulomas [56]. Specifically, TB patients with AIDS present a dominant granulocytic infiltrate and necrosis without the typical caseous necrosis seen in non-HIV-infected TB granulomas. This has been associated with the killing of CD4$^+$ cells in the granuloma, probably resulting in a direct disruption of granuloma structure and abolition of the containment of infection. Cavitary lesions are seldom encountered in patients with a CD4 T-lymphocyte count <200/mm^3 [57]. As a result, while in the majority of adult patients TB is confined preferentially to the lungs, in HIV-infected patients TB can be a systemic disease involving multiple organs that lack well-defined granulomas and instead develop more diffuse lesions [58]. All forms of extrapulmonary TB have been described in patients with HIV.

In macaques, SIV induces distortions in pro-inflammatory and anti-inflammatory T cell responses within the granuloma that may have significant effects on reactivation of latent TB. Reduction of T cell numbers also occurred within lung granulomas of monkeys co-infected with SIV compared with monkeys exclusively infected with TB [59]. It is important to note that besides the known increased risk of disseminated disease in adults with HIV, there is a growing recognition from prevalence surveys of subclinically active TB infection in co-infected individuals [60].

Exacerbation of HIV Infection by *M. tuberculosis* Infection

The incidence and mortality rates for new AIDS-defining opportunistic infections have been shown to be higher if individuals with HIV are co-infected with TB [7,61]. Despite these epidemiological data supporting the notion that *M. tuberculosis* infection has a negative impact on the immune response to HIV and on progression to AIDS, research on possible mechanisms is scarce. The function of many immune cells, including macrophages and DCs, is modulated by both HIV and *M. tuberculosis*. Increased replication of the virus was demonstrated locally, at sites of *M. tuberculosis* infection in the lung [62], and within activated cells, including lymphocytes and CD14$^+$ macrophages, of the pleural space [63] of co-infected patients. *M. tuberculosis* has been reported to up-regulate HIV-1 replication in chronically or acutely infected T cells or macrophages [64,65], as well as ex vivo in alveolar macrophages and lymphocytes from patients with HIV [66,67]. These in vitro/ex vivo findings are also reflected in vivo where elevated plasma viral loads have been detected in HIV-infected individuals with concomitant active TB disease [68].

The primary target for *M. tuberculosis*, the alveolar macrophage, can also be infected with HIV [69–71]. Mycobacteria exacerbate HIV replication in macrophages and lung cells obtained by bronchoalveolar lavage from co-infected individuals [62,65,72]. Also, in vitro studies have demonstrated that *M. tuberculosis* infection can up-regulate both HIV infection and replication within monocyte-derived macrophages (MDMs), increase the efficiency of virus transmission from infected MDMs to T cells, and favor replication of X4 HIV variants by up-regulation of CXCR4 [73]. Furthermore, monocytes from HIV$^+$ patients display an impaired response to TLR ligands [74], and viral proteins can interfere with both MDM and DC maturation and function in vitro, including their ability to phagocytose mycobacteria and kill intracellular bacteria [75–78]. SOCS1, which is stimulated by infection with *M. tuberculosis* [45], has been shown to facilitate the late replication pathways of HIV infection [79] and mediate viral evasion of type I IFN anti-viral signalling [80].

While TNF production in response to *M. tuberculosis* infection is required for control of bacterial growth, TNF is known to activate HIV replication in macrophages [81], indicating that the host immune response initiated against one pathogen may promote the replication of another. Thus, both HIV and *M. tuberculosis* stimulate TNF release from infected cells, and TNF hampers bacterial growth while enhancing HIV replication.

M. tuberculosis survives in DCs and actively down-regulates their pro-inflammatory activity and antigen-presenting function, with concurrent induction of anti-inflammatory cytokines [82]. Similarly, HIV can infect and also manipulate DCs and the ensuing T cell functions [83]. In HIV infection, not only is DC-mediated activation of T cells impaired, but the migration of infected DCs can also contribute to pathogen dissemination.

The DC-expressed C-type lectin receptor DC-SIGN (DC-specific intercellular-adhesion-molecule-3-grabbing nonintegrin) has been suggested to facilitate transmission and immune escape of both *M. tuberculosis* and HIV [84]. HIV attaches to DC-SIGN through interaction with the viral envelope glycoprotein gp120, and this interaction is thought to contribute to efficient spread and transmission of the virus to CD4$^+$ T cells in *trans* [85,86]. *M. tuberculosis* has been reported to target DC-SIGN by a mechanism that is distinct from that of HIV, leading to inhibition of pro-inflammatory IL-12 and TNF production and induction of IL-10 by DCs [87] and, hence, down-regulation of protective immune responses.

It has been suggested that TB patients have a microenvironment that facilitates HIV infection by *i*) increasing the expression of co-receptors CXCR4 and CCR5 regulated by *M. tuberculosis* products; *ii*) increasing pro-inflammatory cytokines, especially TNF; and *iii*) down-regulation of CCL5 [45]. It has also been shown that *M. tuberculosis* and its cell wall component, lipoarabinomannan (LAM) [88], may activate replication of HIV in provirus-carrying cells by inducing TNF and IL-6 production through the NF-κB pathway, which in turn triggers transcriptional activation of the long terminal repeat (LTR) promoter and supports replication of HIV [5].

Immune Reconstitution Inflammatory Syndrome

A particularly intriguing phenomenon is immune reconstitution inflammatory syndrome (IRIS). IRIS may develop in *M. tuberculosis* and HIV co-infected patients who undergo anti-TB treatment and antiretroviral therapy (ART) [89,90]. The definition of IRIS in TB/HIV co-infected patients is still debated [91]. The patients present with an exacerbation of symptoms and radiological manifestations of TB, and recognized predictors of IRIS include low CD4$^+$ T lymphocyte counts and high plasma viral load prior to initiation of ART, and an increase in CD4$^+$ counts after highly active antiretroviral therapy (HAART) onset [92]. Possible mechanisms responsible for IRIS may be a sustained Th1-response against mycobacterial antigens, which is followed by dysregulation of cytokine secretion and T cell migration to the inflammatory site [93]. Recently, it was shown that patients who developed IRIS had higher pre-ART levels of TNF and increasing levels of inflammation biomarkers [94]. Moreover, it has been demonstrated that TB/HIV co-infected patients who experienced IRIS had significantly lower levels of Abs to the phenolic glycolipid (PGL-TB1) antigen, specific for *M. tuberculosis*, compared to patients who did not develop TB-IRIS [95].

Animal Models to Study *M. tuberculosis* and HIV Co-Infection

One of the most important challenges in studies of co-infection is to identify appropriate animal models, since HIV does not cause disease in rodents or even non-human primates. Thus, while mice are ideal models to study immune response to infection and vaccination due to the large diversity of tools and knowledge about their immune system, conventional mice are not susceptible to HIV infection owing to the restricted specificity of the virus for the human cell. To circumvent this limitation, two complementary mouse models were recently generated. Using these models, the most relevant features of *M. tuberculosis* and HIV infections can be reproduced in mice (e.g., typical TB granuloma formation; virus replication in splenic lymphocytes, peritoneal macrophages, and brain; immune exhaustion and/or chronic immune activation; and susceptibility to systemic, vaginal, and rectal HIV infection).

In one, the "humanized mouse", human hematopoietic progenitor cells (CD34$^+$) from human cord blood are used to reconstitute the immune system of immunodeficient mice [96]. A variation of this model incorporates the engraftment of a fetal human thymus fragment, which gains activity as a functional human thymus, allowing a more proper positive and negative T cell selection than the original model [97]. Features such as CD4$^+$ cell depletion, prolonged viremia, and co-receptor-mediated tropism were observed during HIV infection of humanized mice [97–101]. These mice show transplanted human cells in mucosal surfaces and could thereby be infected by the intravaginal and intrarectal routes [102]. The model has been used to evaluate new approaches to the prevention or treatment of HIV infection, including human-neutralizing Abs [102], prophylactic usage of antiretrovirals [98], and T cell–specific siRNA delivery [103]. Inoculation of humanized mice with mycobacteria enhances the CD4/CD8 cell ratio, the differentiation of CD4$^+$ cells into memory/effector types, and the translocation of IFN-γ-secreting T cells into the lung. Of particular importance is that lungs and livers from infected mice show typical features of mycobacterial granuloma (F. Heuts, D. Gavier Widén, B. Carow, J. Juarez, H. Wigzell, et al., unpublished data). On the negative side, the adaptive immune responses, especially the specific IgG levels in response to immunization or infection, are low.

The other mouse model used to study *M. tuberculosis*/HIV interaction, the "EcoHIV" model, makes use of a modified HIV-1 strain, in which the coding region of gp120 has been replaced by that of gp80 from ecotropic murine leukemia virus, that is able to infect the immune cells of conventional mice [104]. The resulting chimeric virus construct, EcoHIV, productively infects immuno-competent mice. Replicating virus is detected in splenic lympho-cytes, peritoneal macrophages, and the brain of mice. The chimeric virus also elicits an immune response directed against viral proteins, and stimulates mouse genes similar to those stimulated by HIV in humans. This murine model of HIV infection has proven useful in vaccine challenge studies and for preclinical evaluation of antiretroviral drugs [105–107].

HIV transgenic mice incorporating the entire viral genome have also been used to study the effect of *M. tuberculosis* infection on the induction of HIV gene expression [108]. In this model, viral gene expression was activated by *M. tuberculosis* and suppressed after anti-mycobacterial chemotherapy [108].

Although non-human primates are resistant to infection by HIV, they can be infected by SIV, a retrovirus causing immunodeficiency similar to AIDS in Asian macaques. Thus, SIV infection in macaques has been used as a model for AIDS. Macaques also develop TB that is very similar to TB in humans, and can develop cavitary lung disease and necrotic lesions. They also can maintain TB latency for years, and only a small proportion of latently infected macaques develop reactivation [56]. Macaques infected with SIV can develop persistent *Mycobacterium bovis* bacillus Calmette Guerin (BCG) [109] and *M. tuberculosis* co-infection [59,110]. Co-infection with SIV and BCG accelerated progression to AIDS [111] and coincided with a severe depletion of CD4$^+$ T cells, loss of BCG-specific T cell responses, and reactivation of the clinically latent BCG infection into a TB-like disease [112]. *M. tuberculosis* reactivation in SIV-infected macaques is associated with early peripheral T cell depletion and not virus load [59].

Summary and Perspectives

TB/HIV co-infection represents a novel pathogenic scenario at the global level. It constitutes a serious diagnostic and therapeutic challenge and, particularly in poor countries, weighs heavily on already strained health care budgets. It has recently been realized that the epidemiology, clinical manifestations, and management of both HIV and *M. tuberculosis* infections are different and far more complex in co-infected compared to mono-infected patients. However, our knowledge about the mechanisms of interaction of the two pathogens still has many gaps that need to be filled in order to develop preventive measures against the two diseases (Box 1).

Ultimately, the most cost-effective way of combating the two diseases would be vaccination. The present TB vaccine, BCG, does not effectively prevent the most prevalent form of the disease, pulmonary TB in adults. Similarly, no effective, preventive HIV vaccine can be discerned on the horizon, although many vaccine candidates are being evaluated in clinical trials. One approach would be to construct a combined TB/HIV vaccine [113], such as a recombinant BCG vaccine as a vehicle for combinations of mycobacterial and HIV antigens.

The design of candidate vaccines is, however, a particularly difficult task since laboratory correlates of protection have not been defined for *M. tuberculosis* and HIV infections. In addition, vaccine-induced immune responses need to be tipped towards protection, avoiding those that may result in immunopathology; this requires meticulous study of appropriate adjuvants, antigens, and vaccination regimens for the novel vaccines. Here the immunomodulatory role of individual antigens of the two pathogens needs further elucidation. For example, the major HIV antigen gp120 [114] and mycobacterial compounds such as glycolipids of the cell wall, particularly LAMs, PIMs, and phenolic glycolipids [115], 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 [53,115,116].

Since both pathogens enter the host through mucosal surfaces, a combination vaccine given at mucosal sites would probably be optimal [117–119]. However, for this, further research in the biology of concurrent *M. tuberculosis* and HIV infections is urgently needed, using in vitro systems, animal models, and clinical studies, as well as vaccine trials.

> **Box 1. Scientific and Technological Objectives for Integrating Knowledge in the Field of Co-Infections with HIV and *M. tuberculosis***
>
> - Development of standardized in vitro and in vivo models for studies of co-infections
> - Interactions and receptor signalling in dendritic cells
> - HIV/*M. tuberculosis*-specific T/B cell responses
> - Role of memory T cells in the maintenance of latent infection and of regulatory T cells in disease outbreak
> - Effector mechanisms of T cells involved in protection against TB
> - The role of antimicrobial peptides in cytolytic T cells
> - Regulation of T cell differentiation during co-infection
> - Immunological synapse; interactions of T and antigen-presenting cells
> - Mathematical modelling and simulation of T, B, and NK cell repertoires
> - Mechanisms of HIV–TB interactions in IRIS
> - The role of individual HIV/*M. tuberculosis* antigens/molecules in immunopathology
> - Effect on immune response in infected individuals after vaccination with TB and/or HIV vaccine candidates

Thus, an integrated approach to the two diseases should 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.

References

1. World Health Organization (2010) Global tuberculosis control 2010. Available: http://www.who.int/tb/publications/global_report/2010/en/index.html. Accessed 13 January 2012.
2. UNAIDS (2010) Chapter 2: epidemic update. UNAIDS report on the global AIDS epidemic 2010. Available: http://www.unaids.org/documents/20101123_GlobalReport_Chap2_em.pdf. Accessed 13 January 2012.
3. Getahun H, Gunneberg C, Granich R, Nunn P (2010) HIV infection-associated tuberculosis: the epidemiology and the response. Clin Infect Dis 50 Suppl 3: S201–S207.
4. Corbett EL, Watt CJ, Walker N, Maher D, Williams BG, et al. (2003) The growing burden of tuberculosis: global trends and interactions with the HIV epidemic. Arch Intern Med 163: 1009–1021.
5. Collins KR, Quinones-Mateu ME, Toossi Z, Arts EJ (2002) Impact of tuberculosis on HIV-1 replication, diversity, and disease progression. AIDS Rev 4: 165–176.
6. Selwyn PA, Hartel D, Lewis VA, Schoenbaum EE, Vermund SH, et al. (1989) A prospective study of the risk of tuberculosis among intravenous drug users with human immunodeficiency virus infection. N Engl J Med 320: 545–550.
7. Whalen C, Horsburgh CR, Hom D, Lahart C, Simberkoff M, et al. (1995) Accelerated course of human immunodeficiency virus infection after tuberculosis. Am J Respir Crit Care Med 151: 129–135.
8. Modjarrad K, Vermund SH (2010) Effect of treating co-infections on HIV-1 viral load: a systematic review. Lancet Infect Dis 10: 455–463.
9. Moller M, Hoal EG (2010) Current findings, challenges and novel approaches in human genetic susceptibility to tuberculosis. Tuberculosis (Edinb) 90: 71–83.
10. MacMicking JD, North RJ, LaCourse R, Mudgett JS, Shah SK, et al. (1997) Identification of nitric oxide synthase as a protective locus against tuberculosis. Proc Natl Acad Sci U S A 94: 5243–5248.
11. Walker L, Lowrie DB (1981) Killing of Mycobacterium microti by immunologically activated macrophages. Nature 293: 69–71.
12. MacMicking JD, Taylor GA, McKinney JD (2003) Immune control of tuberculosis by IFN-gamma-inducible LRG-47. Science 302: 654–659.
13. Chackerian AA, Alt JM, Perera TV, Dascher CC, Behar SM (2002) Dissemination of Mycobacterium tuberculosis is influenced by host factors and precedes the initiation of T-cell immunity. Infect Immun 70: 4501–4509.
14. Cooper AM (2009) T cells in mycobacterial infection and disease. Curr Opin Immunol 21: 378–384.
15. North RJ, Jung YJ (2004) Immunity to tuberculosis. Annu Rev Immunol 22: 599–623.
16. Flynn JL, Goldstein MM, Triebold KJ, Koller B, Bloom BR (1992) Major histocompatibility complex class I-restricted T cells are required for resistance to Mycobacterium tuberculosis infection. Proc Natl Acad Sci U S A 89: 12013–12017.
17. Feng CG, Bean AG, Hooi H, Briscoe H, Britton WJ (1999) Increase in gamma interferon-secreting CD8(+), as well as CD4(+), T cells in lungs following aerosol infection with Mycobacterium tuberculosis. Infect Immun 67: 3242–3247.
18. Ladel CH, Blum C, Dreher A, Reifenberg K, Kaufmann SH (1995) Protective role of gamma/delta T cells and alpha/beta T cells in tuberculosis. Eur J Immunol 25: 2877–2881.
19. Lazarevic V, Flynn J (2002) CD8+ T cells in tuberculosis. Am J Respir Crit Care Med 166: 1116–1121.
20. Orme IM, Roberts AD, Griffin JP, Abrams JS (1993) Cytokine secretion by CD4 T lymphocytes acquired in response to Mycobacterium tuberculosis infection. J Immunol 151: 518–525.
21. Chan J, Flynn J (2004) The immunological aspects of latency in tuberculosis. Clin Immunol 110: 2–12.
22. Kallenius G, Pawlowski A, Brandtzaeg P, Svenson S (2007) Should a new tuberculosis vaccine be administered intranasally? Tuberculosis (Edinb) 87: 257–266.
23. Hess C, Altfeld M, Thomas SY, Addo MM, Rosenberg ES, et al. (2004) HIV-1 specific CD8+ T cells with an effector phenotype and control of viral replication. Lancet 363: 863–866.
24. Streeck H, Brumme ZL, Anastario M, Cohen KW, Jolin JS, et al. (2008) Antigen load and viral sequence diversification determine the functional profile of HIV-1-specific CD8+ T cells. PLoS Med 5: e100. doi:10.1371/journal.pmed.0050100.
25. Euler Z, van Gils MJ, Bunnik EM, Phung P, Schweighardt B, et al. (2010) Cross-reactive neutralizing humoral immunity does not protect from HIV type 1 disease progression. J Infect Dis 201: 1045–1053.
26. Brenchley JM, Douek DC (2008) HIV infection and the gastrointestinal immune system. Mucosal Immunol 1: 23–30.
27. Moir S, Chun TW, Fauci AS (2011) Pathogenic mechanisms of HIV disease. Annu Rev Pathol 6: 223–248.
28. Kanwar B, Favre D, McCune JM (2010) Th17 and regulatory T cells: implications for AIDS pathogenesis. Curr Opin HIV AIDS 5: 151–157.
29. Brenchley JM, Price DA, Schacker TW, Asher TE, Silvestri G, et al. (2006) Microbial translocation is a cause of systemic immune activation in chronic HIV infection. Nat Med 12: 1365–1371.
30. Fitzgerald-Bocarsly P, Jacobs ES (2010) Plasmacytoid dendritic cells in HIV infection: striking a delicate balance. J Leukoc Biol 87: 609–620.
31. Schmitz JE, Kuroda MJ, Santra S, Sasseville VG, Simon MA, et al. (1999) Control of viremia in simian immunodeficiency virus infection by CD8+ lymphocytes. Science 283: 857–860.
32. Miura T, Brockman MA, Schneidewind A, Lobritz M, Pereyra F, et al. (2009) HLA-B57/B*5801 human immunodeficiency virus type 1 elite controllers select for rare gag variants associated with reduced viral replication capacity and strong cytotoxic T-lymphocyte [corrected] recognition. J Virol 83: 2743–2755.
33. Hersperger AR, Pereyra F, Nason M, Demers K, Sheth P, et al. (2010) Perforin expression directly ex vivo by HIV-specific CD8 T-cells is a correlate of HIV elite control. PLoS Pathog 6: e1000917. doi:10.1371/journal.ppat.1000917.
34. Migueles SA, Osborne CM, Royce C, Compton AA, Joshi RP, et al. (2008) Lytic granule loading of CD8+ T cells is required for HIV-infected cell elimination associated with immune control. Immunity 29: 1009–1021.
35. Day CL, Kaufmann DE, Kiepiela P, Brown JA, Moodley ES, et al. (2006) PD-1 expression on HIV-specific T cells is associated with T-cell exhaustion and disease progression. Nature 443: 350–354.
36. Jones RB, Ndhlovu LC, Barbour JD, Sheth PM, Jha AR, et al. (2008) Tim-3 expression defines a novel population of dysfunctional T cells with highly elevated frequencies in progressive HIV-1 infection. J Exp Med 205: 2763–2779.
37. Wang X, Cao Z, Jiang J, Li Y, Dong M, et al. (2011) Elevated expression of Tim-3 on CD8 T cells correlates with disease severity of pulmonary tuberculosis. J Infect 62: 292–300.
38. Dye C, Scheele S, Dolin P, Pathania V, Raviglione MC (1999) Consensus statement. Global burden of tuberculosis: estimated incidence, prevalence, and mortality by country. WHO Global Surveillance and Monitoring Project. JAMA 282: 677–686.
39. Lillebaek T, Dirksen A, Vynnycky E, Baess I, Thomsen VO, et al. (2003) Stability of DNA patterns and evidence of Mycobacterium tuberculosis reactivation occurring decades after the initial infection. J Infect Dis 188: 1032–1039.
40. Aaron L, Saadoun D, Calatroni I, Launay O, Memain N, et al. (2004) Tuberculosis in HIV-infected patients: a comprehensive review. Clin Microbiol Infect 10: 388–398.
41. Lewinsohn DA, Winata E, Swarbrick GM, Tanner KE, Cook MS, et al. (2007) Immunodominant tuberculosis CD8 antigens preferentially restricted by HLA–B. PLoS Pathog 3: e127. doi:10.1371/journal.ppat.0030127.
42. Lewinsohn DA, Heinzel AS, Gardner JM, Zhu L, Alderson MR, et al. (2003) Mycobacterium tuberculosis-specific CD8+ T cells preferentially recognize heavily infected cells. Am J Respir Crit Care Med 168: 1346–1352.
43. van Pinxteren LA, Ravn P, Agger EM, Pollock J, Andersen P (2000) Diagnosis of tuberculosis based on the two specific antigens ESAT-6 and CFP10. Clin Diagn Lab Immunol 7: 155–160.
44. Chen CY, Huang D, Wang RC, Shen L, Zeng G, et al. (2009) A critical role for CD8 T cells in a nonhuman primate model of tuberculosis. PLoS Pathog 5: e1000392. doi:10.1371/journal.ppat.1000392.
45. Rosas-Taraco AG, Arce-Mendoza AY, Caballero-Olin G, Salinas-Carmona MC (2006) Mycobacterium tuberculosis upregulates coreceptors CCR5 and CXCR4 while HIV modulates CD14 favoring concurrent infection. AIDS Res Hum Retroviruses 22: 45–51.
46. Spear GT, Kessler HA, Rothberg L, Phair J, Landay AL (1990) Decreased oxidative burst activity of monocytes from asymptomatic HIV-infected individuals. Clin Immunol Immunopathol 54: 184–191.
47. Wahl SM, Allen JB, Gartner S, Orenstein JM, Popovic M, et al. (1989) HIV-1 and its envelope glycoprotein down-regulate chemotactic ligand receptors and chemotactic function of peripheral blood monocytes. J Immunol 142: 3553–3559.
48. Havlir DV, Barnes PF (1999) Tuberculosis in patients with human immunodeficiency virus infection. N Engl J Med 340: 367–373.
49. Patel NR, Zhu J, Tachado SD, Zhang H, Wan Z, et al. (2007) HIV impairs TNF-alpha mediated macrophage apoptotic response to Mycobacterium tuberculosis. J Immunol 179: 6973–6980.
50. Roberts T, Beyers N, Aguirre A, Walzl G (2007) Immunosuppression during active tuberculosis is characterized by decreased interferon- gamma production and CD25 expression with elevated forkhead box P3, transforming growth factor- beta , and interleukin-4 mRNA levels. J Infect Dis 195: 870–878.
51. Pearl JE, Khader SA, Solache A, Gilmartin L, Ghilardi N, et al. (2004) IL-27 signaling compromises control of bacterial growth in mycobacteria-infected mice. J Immunol 173: 7490–7496.
52. Bonecini-Almeida MG, Ho JL, Boechat N, Huard RC, Chitale S, et al. (2004) Down-modulation of lung immune responses by interleukin-10 and transform-

ing growth factor beta (TGF-beta) and analysis of TGF-beta receptors I and II in active tuberculosis. Infect Immun 72: 2628–2634.

53. Carow B, Ye X, Gavier-Widen D, Bhuju S, Oehlmann W, et al. (2011) Silencing suppressor of cytokine signaling-1 (SOCS1) in macrophages improves Mycobacterium tuberculosis control in an interferon-gamma (IFN-gamma)-dependent manner. J Biol Chem 286: 26873–26887.

54. Hirsch CS, Hussain R, Toossi Z, Dawood G, Shahid F, et al. (1996) Cross-modulation by transforming growth factor beta in human tuberculosis: suppression of antigen-driven blastogenesis and interferon gamma production. Proc Natl Acad Sci U S A 93: 3193–3198.

55. Di Liberto D, Locati M, Caccamo N, Vecchi A, Meraviglia S, et al. (2008) Role of the chemokine decoy receptor D6 in balancing inflammation, immune activation, and antimicrobial resistance in Mycobacterium tuberculosis infection. J Exp Med 205: 2075–2084.

56. Diedrich CR, Flynn JL (2011) HIV-1/mycobacterium tuberculosis coinfection immunology: how does HIV-1 exacerbate tuberculosis? Infect Immun 79: 1407–1417.

57. Sharma SK, Mohan A, Kadhiravan T (2005) HIV-TB co-infection: epidemiology, diagnosis & management. Indian J Med Res 121: 550–567.

58. de Noronha AL, Bafica A, Nogueira L, Barral A, Barral-Netto M (2008) Lung granulomas from Mycobacterium tuberculosis/HIV-1 co-infected patients display decreased in situ TNF production. Pathol Res Pract 204: 155–161.

59. Diedrich CR, Mattila JT, Klein E, Janssen C, Phuah J, et al. (2010) Reactivation of latent tuberculosis in cynomolgus macaques infected with SIV is associated with early peripheral T cell depletion and not virus load. PLoS ONE 5: e9611. doi:10.1371/journal.pone.0009611.

60. Mtei L, Matee M, Herfort O, Bakari M, Horsburgh CR, et al. (2005) High rates of clinical and subclinical tuberculosis among HIV-infected ambulatory subjects in Tanzania. Clin Infect Dis 40: 1500–1507.

61. Pape JW, Jean SS, Ho JL, Hafner A, Johnson WD, Jr. (1993) Effect of isoniazid prophylaxis on incidence of active tuberculosis and progression of HIV infection. Lancet 342: 268–272.

62. Nakata K, Rom WN, Honda Y, Condos R, Kanegasaki S, et al. (1997) Mycobacterium tuberculosis enhances human immunodeficiency virus-1 replication in the lung. Am J Respir Crit Care Med 155: 996–1003.

63. Lawn SD, Pisell TL, Hirsch CS, Wu M, Butera ST, et al. (2001) Anatomically compartmentalized human immunodeficiency virus replication in HLA-DR+ cells and CD14+ macrophages at the site of pleural tuberculosis coinfection. J Infect Dis 184: 1127–1133.

64. Shattock RJ, Friedland JS, Griffin GE (1993) Modulation of HIV transcription in and release from human monocytic cells following phagocytosis of Mycobacterium tuberculosis. Res Virol 144: 7–12.

65. Zhang Y, Nakata K, Weiden M, Rom WN (1995) Mycobacterium tuberculosis enhances human immunodeficiency virus-1 replication by transcriptional activation at the long terminal repeat. J Clin Invest 95: 2324–2331.

66. Toossi Z, Nicolacakis K, Xia L, Ferrari NA, Rich EA (1997) Activation of latent HIV-1 by Mycobacterium tuberculosis and its purified protein derivative in alveolar macrophages from HIV-infected individuals in vitro. J Acquir Immune Defic Syndr Hum Retrovirol 15: 325–331.

67. Goletti D, Weissman D, Jackson RW, Collins F, Kinter A, et al. (1998) The in vitro induction of human immunodeficiency virus (HIV) replication in purified protein derivative-positive HIV-infected persons by recall antigen response to Mycobacterium tuberculosis is the result of a balance of the effects of endogenous interleukin-2 and proinflammatory and antiinflammatory cyto-kines. J Infect Dis 177: 1332–1338.

68. Goletti D, Weissman D, Jackson RW, Graham NM, Vlahov D, et al. (1996) Effect of Mycobacterium tuberculosis on HIV replication. Role of immune activation. J Immunol 157: 1271–1278.

69. Nakata K, Weiden M, Harkin T, Ho D, Rom WN (1995) Low copy number and limited variability of proviral DNA in alveolar macrophages from HIV-1-infected patients: evidence for genetic differences in HIV-1 between lung and blood macrophage populations. Mol Med 1: 744–757.

70. Landay AL, Schade SZ, Takefman DM, Kuhns MC, McNamara AL, et al. (1993) Detection of HIV-1 provirus in bronchoalveolar lavage cells by polymerase chain reaction. J Acquir Immune Defic Syndr 6: 171–175.

71. Sierra-Madero JG, Toossi Z, Hom DL, Finegan CK, Hoenig E, et al. (1994) Relationship between load of virus in alveolar macrophages from human immunodeficiency virus type 1-infected persons, production of cytokines, and clinical status. J Infect Dis 169: 18–27.

72. Orenstein JM, Fox C, Wahl SM (1997) Macrophages as a source of HIV during opportunistic infections. Science 276: 1857–1861.

73. Mancino G, Placido R, Bach S, Mariani F, Montesano C, et al. (1997) Infection of human monocytes with Mycobacterium tuberculosis enhances human immunodeficiency virus type 1 replication and transmission to T cells. J Infect Dis 175: 1531–1535.

74. Jiang W, Lederman MM, Salkowitz JR, Rodriguez B, Harding CV, et al. (2005) Impaired monocyte maturation in response to CpG oligodeoxynucleo-tide is related to viral RNA levels in human immunodeficiency virus disease and is at least partially mediated by deficiencies in alpha/beta interferon responsiveness and production. J Virol 79: 4109–4119.

75. Kedzierska K, Mak J, Mijch A, Cooke I, Rainbird M, et al. (2000) Granulocyte-macrophage colony-stimulating factor augments phagocytosis of Mycobacterium avium complex by human immunodeficiency virus type 1-

76. Biggs BA, Hewish M, Kent S, Hayes K, Crowe SM (1995) HIV-1 infection of human macrophages impairs phagocytosis and killing of Toxoplasma gondii. J Immunol 154: 6132–6139.

77. Sacchi A, Cappelli G, Cairo C, Martino A, Sanarico N, et al. (2007) Differentiation of monocytes into CD1a- dendritic cells correlates with disease progression in HIV-infected patients. J Acquir Immune Defic Syndr 46: 519–528.

78. Muthumani K, Hwang DS, Choo AY, Mayilvahanan S, Dayes NS, et al. (2005) HIV-1 Vpr inhibits the maturation and activation of macrophages and dendritic cells in vitro. Int Immunol 17: 103–116.

79. Ryo A, Tsurutani N, Ohba K, Kimura R, Komano J, et al. (2008) SOCS1 is an inducible host factor during HIV-1 infection and regulates the intracellular trafficking and stability of HIV-1 Gag. Proc Natl Acad Sci U S A 105: 294–299.

80. Fenner JE, Starr R, Cornish AL, Zhang JG, Metcalf D, et al. (2006) Suppressor of cytokine signaling 1 regulates the immune response to infection by a unique inhibition of type I interferon activity. Nat Immunol 7: 33–39.

81. Kedzierska K, Crowe SM, Turville S, Cunningham AL (2003) The influence of cytokines, chemokines and their receptors on HIV-1 replication in monocytes and macrophages. Rev Med Virol 13: 39–56.

82. Jiao X, Lo-Man R, Guermonprez P, Fiette L, Deriaud E, et al. (2002) Dendritic cells are host cells for mycobacteria in vivo that trigger innate and acquired immunity. J Immunol 168: 1294–1301.

83. Donaghy H, Stebbing J, Patterson S (2004) Antigen presentation and the role of dendritic cells in HIV. Curr Opin Infect Dis 17: 1–6.

84. van Kooyk Y, Appelmelk B, Geijtenbeek TB (2003) A fatal attraction: Mycobacterium tuberculosis and HIV-1 target DC-SIGN to escape immune surveillance. Trends Mol Med 9: 153–159.

85. Geijtenbeek TB, Kwon DS, Torensma R, van Vliet SJ, van Duijnhoven GC, et al. (2000) DC-SIGN, a dendritic cell-specific HIV-1-binding protein that enhances trans-infection of T cells. Cell 100: 587–597.

86. Kwon DS, Gregorio G, Bitton N, Hendrickson WA, Littman DR (2002) DC-SIGN-mediated internalization of HIV is required for trans-enhancement of T cell infection. Immunity 16: 135–144.

87. Geijtenbeek TB, Van Vliet SJ, Koppel EA, Sanchez-Hernandez M, Vanden-broucke-Grauls CM, et al. (2003) Mycobacteria target DC-SIGN to suppress dendritic cell function. J Exp Med 197: 7–17.

88. Briken V, Porcelli SA, Besra GS, Kremer L (2004) Mycobacterial lipoarabinomannan and related lipoglycans: from biogenesis to modulation of the immune response. Mol Microbiol 53: 391–403.

89. Lawn SD, Bekker LG, Miller RF (2005) Immune reconstitution disease associated with mycobacterial infections in HIV-infected individuals receiving antiretrovirals. Lancet Infect Dis 5: 361–373.

90. Muller M, Wandel S, Colebunders R, Attia S, Furrer H, et al. (2010) Immune reconstitution inflammatory syndrome in patients starting antiretroviral therapy for HIV infection: a systematic review and meta-analysis. Lancet Infect Dis 10: 251–261.

91. Meintjes G, Lawn SD, Scano F, Maartens G, French MA, et al. (2008) Tuberculosis-associated immune reconstitution inflammatory syndrome: case definitions for use in resource-limited settings. Lancet Infect Dis 8: 516–523.

92. Breton G, Duval X, Estellat C, Poaletti X, Bonnet D, et al. (2004) Determinants of immune reconstitution inflammatory syndrome in HIV type 1-infected patients with tuberculosis after initiation of antiretroviral therapy. Clin Infect Dis 39: 1709–1712.

93. Bourgarit A, Carcelain G, Martinez V, Lascoux C, Delcey V, et al. (2006) Explosion of tuberculin-specific Th1-responses induces immune restoration syndrome in tuberculosis and HIV co-infected patients. AIDS 20: F1–7.

94. Boulware DR, Hullsiek KH, Puronen CE, Rupert A, Baker JV, et al. (2011) Higher levels of CRP, D-dimer, IL-6, and hyaluronic acid before initiation of antiretroviral therapy (ART) are associated with increased risk of AIDS or death. J Infect Dis 203: 1637–1646.

95. Simonney N, Dewulf G, Herrmann JL, Gutierrez MC, Vicaut E, et al. (2008) Anti-PGL-Tb1 responses as an indicator of the immune restoration syndrome in HIV-TB patients. Tuberculosis (Edinb) 88: 453–461.

96. Traggiai E, Chicha L, Mazzucchelli L, Bronz L, Piffaretti JC, et al. (2004) Development of a human adaptive immune system in cord blood cell-transplanted mice. Science 304: 104–107.

97. Gorantla S, Makarov E, Finke-Dwyer J, Gebhart CL, Domm W, et al. (2010) CD8+ cell depletion accelerates HIV-1 immunopathology in humanized mice. J Immunol 184: 7082–7091.

98. Denton PW, Krisko JF, Powell DA, Mathias M, Kwak YT, et al. (2010) Systemic administration of antiretrovirals prior to exposure prevents rectal and intravenous HIV-1 transmission in humanized BLT mice. PLoS ONE 5: e8829. doi:10.1371/journal.pone.0008829.

99. Sun Z, Denton PW, Estes JD, Othieno FA, Wei BL, et al. (2007) Intrarectal transmission, systemic infection, and CD4+ T cell depletion in humanized mice infected with HIV-1. J Exp Med 204: 705–714.

100. Zhang L, Kovalev GI, Su L (2007) HIV-1 infection and pathogenesis in a novel humanized mouse model. Blood 109: 2978–2981.

101. Baenziger S, Tussiwand R, Schlaepfer E, Mazzucchelli L, Heikenwalder M, et al. (2006) Disseminated and sustained HIV infection in CD34+ cord blood cell-

transplanted Rag2−/−gamma c−/− mice. Proc Natl Acad Sci U S A 103: 15951–15956.

102. Joseph A, Zheng JH, Chen K, Dutta M, Chen C, et al. (2010) Inhibition of in vivo HIV infection in humanized mice by gene therapy of human hematopoietic stem cells with a lentiviral vector encoding a broadly neutralizing anti-HIV antibody. J Virol 84: 6645–6653.

103. Kumar P, Ban HS, Kim SS, Wu H, Pearson T, et al. (2008) T cell-specific siRNA delivery suppresses HIV-1 infection in humanized mice. Cell 134: 577–586.

104. Potash MJ, Chao W, Bentsman G, Paris N, Saini M, et al. (2005) A mouse model for study of systemic HIV-1 infection, antiviral immune responses, and neuroinvasiveness. Proc Natl Acad Sci U S A 102: 3760–3765.

105. Roshorm Y, Hong JP, Kobayashi N, McMichael AJ, Volsky DJ, et al. (2009) Novel HIV-1 clade B candidate vaccines designed for HLA-B*5101(+) patients protected mice against chimaeric ecotropic HIV-1 challenge. Eur J Immunol 39: 1831–1840.

106. Saini M, Hadas E, Volsky DJ, Potash MJ (2007) Vaccine-induced protection from infection of mice by chimeric human immunodeficiency virus type 1, EcoHIV/NL4-3. Vaccine 25: 8660–8663.

107. Hadas E, Borjabad A, Chao W, Saini M, Ichiyama K, et al. (2007) Testing antiretroviral drug efficacy in conventional mice infected with chimeric HIV-1. AIDS 21: 905–909.

108. Scanga CA, Bafica A, Sher A (2007) Viral gene expression in HIV transgenic mice is activated by Mycobacterium tuberculosis and suppressed after antimycobacterial chemotherapy. J Infect Dis 195: 246–254.

109. Shen Y, Zhou D, Chalifoux L, Shen L, Simon M, et al. (2002) Induction of an AIDS virus-related tuberculosis-like disease in macaques: a model of simian immunodeficiency virus- mycobacterium coinfection. Infect Immun 70: 869–877.

110. Safi H, Gormus BJ, Didier PJ, Blanchard JL, Lakey DL, et al. (2003) Spectrum of manifestations of Mycobacterium tuberculosis infection in primates infected with SIV. AIDS Res Hum Retroviruses 19: 585–595.

111. Zhou D, Shen Y, Chalifoux L, Lee-Parritz D, Simon M, et al. (1999) Mycobacterium bovis bacille Calmette-Guerin enhances pathogenicity of simian immunodeficiency virus infection and accelerates progression to AIDS in macaques: a role of persistent T cell activation in AIDS pathogenesis. J Immunol 162: 2204–2216.

112. Shen Y, Shen L, Sehgal P, Huang D, Qiu L, et al. (2004) Clinical latency and reactivation of AIDS-related mycobacterial infections. J Virol 78: 14023–14032.

113. Kaufmann SH, McMichael AJ (2005) Annulling a dangerous liaison: vaccination strategies against AIDS and tuberculosis. Nat Med 11: S33–S44.

114. Del Corno M, Liu QH, Schols D, de Clercq E, Gessani S, et al. (2001) HIV-1 gp120 and chemokine activation of Pyk2 and mitogen-activated protein kinases in primary macrophages mediated by calcium-dependent, pertussis toxin-insensitive chemokine receptor signaling. Blood 98: 2909–2916.

115. Portevin D, Gagneux S, Comas I, Young D (2011) Human macrophage responses to clinical isolates from the Mycobacterium tuberculosis complex discriminate between ancient and modern lineages. PLoS Pathog 7: e1001307. doi:10.1371/journal.ppat.1001307.

116. Locher CP, Witt SA, Kassel R, Dowell NL, Fujimura S, et al. (2005) Differential effects of R5 and X4 human immunodeficiency virus type 1 infection on CD4+ cell proliferation and activation. J Gen Virol 86: 1171–1179.

117. Hiroi T, Goto H, Someya K, Yanagita M, Honda M, et al. (2001) HIV mucosal vaccine: nasal immunization with rBCG–V3J1 induces a long term V3J1 peptide-specific neutralizing immunity in Th1- and Th2-deficient conditions. J Immunol 167: 5862–5867.

118. Kawahara M, Hashimoto A, Toida I, Honda M (2002) Oral recombinant Mycobacterium bovis bacillus Calmette-Guerin expressing HIV-1 antigens as a freeze-dried vaccine induces long-term, HIV-specific mucosal and systemic immunity. Clin Immunol 105: 326–331.

119. Yu JS, Peacock JW, Jacobs WR, Jr., Frothingham R, Letvin NL, et al. (2007) Recombinant Mycobacterium bovis bacillus Calmette-Guerin elicits human immunodeficiency virus type 1 envelope-specific T lymphocytes at mucosal sites. Clin Vaccine Immunol 14: 886–893.