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Respiratory Infection Complicating HIV Infection

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Abstract

Purpose of review—Respiratory infections remain a major cause of morbidity among HIV-infected persons. Thus, an up-to-date knowledge of recent advances regarding HIV-associated opportunistic pneumonias is crucial to the optimal care of persons with HIV.

Recent findings—Bacterial pneumonia is the most common HIV-associated opportunistic pneumonia in the United States and its incidence remains appreciable. Worldwide, tuberculosis (TB) dominates the clinical picture. The absence of rapid, affordable diagnostics for active and latent TB remains a major obstacle that must be overcome for the global epidemic to be slowed. The specter of extensively-drug-resistant (XDR) TB and its overlap with HIV infection highlight the importance of rapid diagnostics and the need for accessible drug susceptibility testing. *Pneumocystis* pneumonia (PCP) appears to be a more common etiology among HIV-infected persons residing in developing countries than previously appreciated. Similar to TB, the absence of available diagnostics in developing areas is a major obstacle to clinical care and epidemiologic studies. The critical care of HIV-infected persons is challenging.

Summary—Although tremendous advances in our understanding of the management, treatment, and prevention of HIV and its associated respiratory infections have been made, significant gaps remain. Thus, continued epidemiologic, clinical, and bench research is needed.

Keywords

HIV/AIDS; bacterial pneumonia; tuberculosis (TB); *Pneumocystis* pneumonia (PCP); critical care

Abbreviations

AFB; ART; BAL; CFP-10; ESAT-6; ICU; IDU; IPT; IRIS; MDR; MODS; NNRTI; PCP; PCR; PPV; QFT; TB; TMP-SMZ; TIGRA; TST; USPHS/IDSA; XDR

INTRODUCTION

While dramatic improvements in long-term survival have continued to accrue to those living with HIV in the United States, those benefits have yet to extend to the developing world, where a large proportion of those with HIV continue to die, many with opportunistic respiratory infections and most without the benefit of either accurate diagnosis or treatment. As a consequence of these trends, the focus of many researchers has shifted internationally,

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a fact which is reflected in the articles reviewed here. Yet, in spite of changes in the location of the epidemic, the fundamental principles of management of HIV-associated respiratory diseases–confirming diagnoses, anticipating co-existent disease processes, and reconstituting immunity-remain operative, although resource considerations factor into clinical and policy decisions now more than ever.

Organizing our discussion around the principal opportunistic respiratory pathogens, we review the most important articles published on HIV-associated pulmonary infections and their management during 2006 and the first three-quarters of 2007.

BACTERIAL PNEUMONIA

Bacterial pneumonia is the most common HIV-associated opportunistic pneumonia in the United States and its incidence remains appreciable.

Incidence

Following the introduction of combination antiretroviral therapy (ART), the relative incidence of HIV-associated pneumonias has changed, with bacterial pneumonia replacing *Pneumocystis* pneumonia (PCP) as the most frequently encountered opportunistic respiratory infection. In a prospective multi-center observational cohort study of HIV-infected women in the United States, Kohli and colleagues report an incidence of bacterial pneumonia of 8.5 cases per 100 person-years in HIV-infected women compared to 0.7 cases per 100 person-years in HIV-negative controls with a history of injection drug use (IDU) or high risk sexual behavior [1]*. Use of ART and trimethoprim-sulfamethoxazole (TMP-SMX) were associated with decreased risk, while lower baseline CD4 count and active cigarette use were associated with increased risk of bacterial pneumonia. Only 25% of HIV-infected cases had a culture result specifying the causal bacterial pathogen. This latter point emphasizes the need for improved diagnostic tests for bacterial pathogens for both clinical care and epidemiological studies.

Pneumococcal vaccination

The US Public Health Service/Infectious Diseases Society of America (USPHS/IDSA) guidelines for prevention of opportunistic infections recommend administration of the 23-valent polysaccharide pneumococcal vaccine (PPV) to HIV-infected individuals with a CD4 count greater than 200 cells/μL. The efficacy of the PPV in reducing pneumococcal pneumonia and invasive disease was studied by Penaranda and colleagues in a case-control study of HIV-infected patients matched for age, gender, CD4 count, and HIV risk factor [2]*. In multivariate analysis, the authors found that use of ART and the PPV were associated with decreased risk of pneumococcal disease, even in subjects whose CD4 count was less than 200 cells/μL. Flannery studied whether the introduction of a pediatric pneumococcal conjugate vaccine in 2000 has been associated with a decreased rate of invasive pneumococcal disease in HIV-infected adults [3]*. They found that rates of invasive pneumococcal disease in both HIV-infected and non-infected adults decreased significantly between 1998 and 2003. However, among HIV-infected persons, the decrease was isolated to pneumococcal serotypes in the pediatric conjugate vaccine, while rates of invasive pneumococcal disease from non-vaccine serotypes actually increased during the same time period. Because the study lacked information on CD4 count and use of ART as well as other relevant factors, a definitive association between the pediatric pneumococcal vaccine and a decrease in adult HIV-associated pneumococcal disease remains to be proven.

VIRAL INFECTIONS

Klein and colleagues prospectively studied a cohort of 50 HIV-infected patients presenting with fever and respiratory symptoms to an outpatient HIV clinic [4]*. The majority (90%) were taking ART, with a median CD4 count of 325 cells/μL (range 2–808). Using nasopharyngeal swabs and serologic data, the authors diagnosed 21 patients (42%) with viral infections (20 with influenza, 1 with parainfluenza) despite a high rate of prior influenza vaccination (76%). The authors concluded that influenza is a common cause of febrile respiratory symptoms in HIV-infected outpatients taking ART, despite the use of the influenza vaccine.

MYCOBACTERIUM TUBERCULOSIS INFECTION

Worldwide, tuberculosis is the most important HIV-associated opportunistic pneumonia.

Diagnosis

The absence of rapid, affordable diagnostics for tuberculosis (TB) remains a major obstacle to identifying disease in susceptible individuals and to gathering reliable population-based estimates of disease burden. This is a major obstacle in management of HIV-infected patients, in whom smear-microscopy performs particularly poorly. In a systematic review of national tuberculosis control program policies, Getahun and colleagues argue for modification of national TB evaluation algorithms to include HIV-testing and risk-stratification by AIDS severity; chest radiography; and, as they become available, rapid diagnostics as a strategy for improving passive case finding [5]*. To compare the impact of rapid diagnostic testing with other novel TB control strategies targeting HIV-infected individuals with active case-finding and ART, Dowdy and colleagues developed mathematical models of expected TB incidence after the introduction of each of these strategies in high HIV-prevalence areas [6]*. They found that rapid diagnostic tests could reduce global TB prevalence and mortality by more than 20% and incidence by 10%, effects that were much greater than those achieved by targeting HIV-infected individuals alone. While many such tests are in development, the only recent clinical studies of these tests have involved T-cell-based interferon-gamma-release assays (TIGRAs).

T-cell-based interferon-gamma-release assays

In the developed world, TIGRAs have begun to supplant the tuberculin skin test (TST) for diagnosis of latent TB infection. TIGRAs quantify interferon-gamma release from peripheral blood T-lymphocytes after overnight incubation with two highly specific TB antigens, early secretory antigen-6 (ESAT-6) and culture filtrate protein-10 (CFP-10). Unfortunately, the popularity of TIGRAs can be attributed more to their hypothetical advantages than to strong clinical evidence of their performance. For example, QuantiFERON (Cellestis, Valencia, CA) is recognized as an alternative to TST in the Centers for Disease Control and Prevention's guidelines [7]**, but there have been few investigations of the test's performance in HIV-infected individuals. Luetkemeyer and colleagues studied second generation QuantiFERON (QFT) responses in a cohort of 294 patients with HIV and found that more than 10% of participants had discordance between TST and QFT results, with TST-positive, QFT-negatives, and TST-negative, QFT-positives equally represented [8]*. Moreover, 5% of those studied had indeterminate results because control lymphocytes failed to respond to phytohemagglutinin, an outcome that was strongly associated with low CD4-count.

For the diagnosis of active disease, the theoretical low specificity of TIGRAs has been the major obstacle to their use. Jafari and colleagues attempted to circumvent the problem of false-positives due to latent TB infection by testing lymphocytes obtained by

bronchoalveolar lavage (BAL), because TB-disease-activated effector T-cells are thought to be expressed in the lung in preference to latent-TB-activated memory T-cells [9]. Using this technique, they showed an enzyme-linked immunospot assay, T.SPOT.*TB* (Oxford Immunotec, Abingdon, Oxon, UK), to be 100% sensitive and 100% specific in 37 patients undergoing evaluation for smear-negative tuberculosis in Germany. This promising approach bears further study in a population-based cohort undergoing evaluation for TB in a high-TB-prevalence setting.

Control and Prevention

A number of authors have attempted to quantify the contribution of the HIV epidemic to the TB epidemic. Wood and colleagues evaluated case-finding rates as reported in a TB treatment register in South Africa by randomly surveying symptoms and collecting sputum for microscopy and culture in a community-based cohort [10]. Their aim was to compare HIV-infected and HIV-uninfected individuals with respect to symptom duration, prevalence, and frequency of diagnosed TB. While the duration of symptoms was similar in the two groups, the case-finding proportion in HIV-infected patients was only 37%, compared to 67% in HIV-uninfected patients. Moreover, HIV-infected individuals contributed 87% of the total person-years of undiagnosed TB, so the authors endorse a policy of active case finding in the HIV-infected population.

In Brazil, Golub and colleagues explored the efficacy of the combination of ART and isoniazid prophylactic therapy (IPT) in a retrospective study of TB incidence in 29 public health clinics [11]*. They found the highest reduction in TB incidence with combined ART and IPT, followed by IPT alone, followed by ART alone, all in comparison to no treatment. In Switzerland, a low TB-prevalence setting, Elzi and colleagues tested a similar screening approach based on use of TST, IPT, and ART in an HIV-infected cohort [12]. While their findings would have been strengthened by sensitivity analyses to exclude the possibility of biased selection of those in the intervention group, the 100% absolute risk reduction associated with the intervention was impressive and bears further study.

Many TB experts have expressed concern over the IPT strategy, fearing it may lead to increased drug-resistance, especially in high HIV- and TB-prevalence areas. In a mathematical model of the impact of IPT, Cohen and colleagues showed while IPT will decrease TB incidence in the short-term, its widespread use is likely to be accompanied by an increase in drug-resistant TB [13]*. Since acquired rifamycin resistance has also been associated with TB treatment in HIV-infected patients, the IPT strategy adds to the theoretical risk of multi-drug resistant (MDR) TB (defined as resistance to both isoniazid and rifampin).

MDR/XDR TB

Perhaps the most frightening recent publication with regard to HIV-TB co-infection is the report of Gandhi and colleagues on an outbreak of extensively-drug-resistant (XDR) TB (defined as MDR TB plus high-level resistance to fluoroquinolones and to second-line injectable anti-TB agents) in a high HIV-prevalence area in South Africa [14]**. After undertaking enhanced surveillance for drug resistance in a rural hospital with sputum culture, routine drug susceptibility testing, and genotyping, these investigators found a 39% MDR prevalence and a 6% XDR prevalence. Of the 44 XDR patients tested for HIV, all were seropositive. All but one of the XDR patients (including several HIV-infected health care workers) died, after a median of 16 days. Most alarmingly, 85% of XDR isolates were of the same genotype, strongly suggesting nosocomial transmission of TB as the cause of the drug-resistance rather than previous treatment. The XDR study of Gandhi and colleagues implies that HIV-infection is a major risk factor for poor outcomes with drug-resistant TB,

and points to the urgent need for rapid, point-of-care drug-susceptibility testing to improve individual outcomes and to decrease transmission. To meet this need, Moore and colleagues have developed a transparent but contained broth-culture system, the Microscopic Observation Drug Susceptibility (MODS) assay, and showed it to be effective in a program setting in Lima, Peru [15]**. In reference to a sample-based, composite microbiological gold standard, MODS was 97% sensitive and 89% specific for growth of MTB. Culture and highly accurate drug-susceptibility results were both available at a median of 7 days. While the requirement for an inverted microscope raises concerns about whether the MODS technology can be transferred to resource-limited settings, these concerns are balanced by the speed, safety, and simplicity of MODS, so studies to test it in other program settings are eagerly anticipated.

Treatment Outcomes in HIV-infected patients

The importance of early and aggressive treatment of both HIV and TB has been emphasized in several of the studies discussed above, but many questions remain unanswered about HIV-TB co-infection. Nahid and colleagues carried out a retrospective study of TB treatment outcomes in 264 HIV-infected patients treated in San Francisco from 1990–2001, and found the relapse rate to be nine times higher in these patients compared to HIV-negative controls treated during the same period [16]*. Longer treatment (9 months versus 6 months) was strongly associated with fewer relapses, and ART was associated with more rapid time to microscopy and culture conversion, as well as improved survival.

Although some of the data about improved outcomes with ART in newly diagnosed TB subjects is impressive, safety concerns related to the practicalities of drug interactions and the immune reconstitution inflammatory syndrome (IRIS) persist. In a small study of South African patients, Friedland and colleagues showed that while serum levels of the non-nucleoside reverse transcriptase inhibitor (NNTRI) efavirenz varied dramatically in patients receiving simultaneous rifampin-based TB-treatment regimens, short-term clinical outcomes were excellent, with 80% cured of TB while achieving undetectable serum HIV RNA and avoiding treatment-limiting hepatotoxicity or neurotoxicity[17]. Larger and longer-term studies are needed to understand the long-term risks of TB relapse, anti-TB-drug resistance, and HIV resistance to NNRTIs. Breen and colleagues found no difference in the proportion with TB relapse in HIV-infected subjects compared to HIV-uninfected subjects with TB, or in the proportion of HIV-TB co-infected patients achieving viral suppression compared to HIV-infected patients without TB [18].

To help clinicians weigh the risks of IRIS, Schiffer and colleagues created a decision-analysis model for evaluating the safety of the early initiation of ART (starting during the first two months of TB treatment) versus delayed ART (starting during the continuation phase) [19]*. Even at the highest reported incidences of IRIS and drug toxicity, they found a no risk and probable benefit to early initiation of ART with respect to the composite endpoint of all–cause mortality, new AIDS-defining illness, and treatment-limiting drug toxicities.

Immune reconstitution inflammatory syndrome

A variety of theories regarding the etiology of IRIS have been proposed, but Bourgarit and colleagues offer the first convincing evidence of its pathophysiology. Among individuals who developed IRIS, they demonstrated dramatic spikes in Th1-related cytokine responses to PPD as well as TB-specific antigens, compared to HIV-TB co-infected controls who initiated ART and anti-TB treatment simultaneously but did not develop IRIS [20]. A clinical history study of TB IRIS from Lawn and colleagues in South Africa demonstrates that nearly a third of patients who initiate ART and TB treatment simultaneously will have

IRIS manifestations (compared to 12% of those who delay ART initiation until the continuation phase of TB treatment) [21]*. These manifestations are usually mild, requiring hospitalization in less than 5% and death in 1%. Respiratory and intra-abdominal symptoms were the most common manifestations of TB IRIS, and the risk increased at lower starting CD4+ T-cell counts.

HIV-TB Co-infection

An excellent overview of the issues surrounding HIV-TB co-infection is contained in a series of articles published in the August, 2007 supplement to the *Journal of Infectious Diseases* [22]**.

PNEUMOCYSTIS PNEUMONIA (PCP)

Pneumocystis pneumonia (PCP) remains the most frequent AIDS-defining opportunistic pneumonia in the United States and is a major cause of mortality.

Recent advances

The American Thoracic Society sponsored a 1-day workshop on “Recent Advances and Future Directions in *Pneumocystis* Pneumonia (PCP),” and a summary of the workshop presentations is published in the *Proceedings of the American Thoracic Society* [23]**.

Prevalence

While PCP remains the most common AIDS-defining illness in the United States, it has been considered a rare disease in Africa. Two recent studies suggest that PCP is more common in Africa than previously thought. In a cohort of Ethiopian HIV-infected patients with respiratory symptoms and sputa smear negative for acid fast bacilli (AFB), Aderaye and colleagues diagnosed 39 of 131 (30%) patients with PCP by immunofluorescence staining [24]*. A South African autopsy study performed by Wong and colleagues found histologic evidence of PCP in the lungs of 328 of 8,421 (3.9%) deceased African miners [25]*. Co-infection was present 33% of the time, most commonly with *Cryptococcus neoformans* or bacterial pneumonia. The rate of PCP infection increased from 9.1 cases per 1000 population in 1996 to 66 cases per 1000 population in 2000, yet the disease was not suspected prior to death in 89% of patients. The rate of HIV infection was not reported in this study, but 25% of South African miners are estimated to be HIV-infected.

Antibiotic prophylaxis

The USPHS/IDSA guidelines for prevention of opportunistic infection in HIV-infected persons recommend antibiotic prophylaxis against PCP until there is a sustained increase in CD4 count above 200 cells/μL. Whether prophylaxis can be safely discontinued in the setting of an undetectable HIV viral load while the CD4 count remains below 200 cells/μL is not known. D’Egidio and colleagues studied a prospective cohort of 19 HIV-infected patients taking ART who had discontinued PCP prophylaxis (for a median of 9 months, range 3–39 months), all with an undetectable HIV viral load and a CD4 count that had plateaued at less than 200 cells/μL (median 120 cells/μL, range 32–184) [26]*. No patients developed PCP in 261 patient-months of follow-up, an incidence significantly lower than the expected rate based on a historical control. Given this study’s limited sample size, additional research is necessary before changing clinical practice based on the HIV viral load.

Molecular diagnosis

Current diagnosis of PCP relies on direct visualization of *Pneumocystis* cysts or trophic forms from stained respiratory specimens. Interest has shifted toward polymerase chain

reaction (PCR) assays, which can be more sensitive than microscopy and require less invasive respiratory specimens such as oropharyngeal wash. While earlier studies have utilized PCR primers to the mitochondrial large subunit ribosomal RNA sequence (mt LSU rRNA), Huggett and colleagues report results from a real-time PCR assay using primers to the heat-shock protein 70 gene (HSP70) [27]*. Their assay, which allows for quantification of pathogen load, showed a sensitivity and specificity of 98% and 96% when used in clinical samples of bronchoalveolar lavage (BAL) fluid from patients who had PCP or an alternative respiratory diagnosis. In comparison, conventional PCR with mt LSU rRNA primers showed similar sensitivity but a lower specificity of only 68% in the same clinical samples. The higher false-positive rates in conventional PCR assays have been attributed to PCP colonization, limiting their utility in accurately diagnosing PCP infection.

Pneumocystis colonization

Pneumocystis colonization is defined as detection of *Pneumocystis*, typically by PCR assay, in respiratory samples in the absence of clinical signs or symptoms of *Pneumocystis* infection. PCP colonization has been described in both HIV-infected persons and non-infected healthy controls, and is particularly prevalent in those who smoke or have underlying obstructive lung disease [28,29]. PCP colonization can occur in subjects who have relatively high CD4 counts, as well as in those who are taking ART and PCP prophylaxis. The clinical significance of PCP colonization is unknown at this time, although research has suggested a role in chronic inflammation and progression of COPD. In addition, subjects who are PCP-colonized may serve as a pathogen reservoir. Norris and colleagues have written an excellent review article summarizing the current state of knowledge on PCP colonization and its potential association with COPD [30]*.

RESPIRATORY INFECTIONS AND INTENSIVE CARE

Respiratory failure secondary to PCP was one of the most common reasons for admission to an intensive care unit (ICU) early in the AIDS epidemic. With the advent of ART, the incidence of PCP and other opportunistic infections has declined dramatically. However, it is unclear whether mortality from severe PCP requiring ICU level care has changed since the introduction of ART. One earlier retrospective study done at San Francisco General Hospital found that the use of ART either before or during an ICU admission for PCP was associated with decreased mortality [31]. In contrast, in a retrospective cohort of HIV-infected patients with severe PCP requiring ICU admission, Miller and colleagues found that mortality from severe PCP was associated with year of PCP diagnosis (mortality 71% before mid 1996, 34% after mid 1996) but not use of antiretroviral therapy [32]**. None of their cohort of 59 patients received ART before or during their admission for severe PCP. They attributed the decline in PCP mortality to general improvements in ICU care for respiratory failure during this time period, including the adoption of low tidal volume ventilation for the acute respiratory distress syndrome.

Overall ICU mortality in HIV-infected patients has declined since the introduction of ART. Two reviews, one by Morris and colleagues [33]* and the other by Huang and colleagues [34]**, address recent developments in intensive care of HIV-infected patients. More patients are admitted to the ICU with non-AIDS related diagnoses and fewer for opportunistic infections or respiratory failure in the ART era. While the use of antiretroviral therapy in the ICU may confer potential benefits, it can be complicated by multiple drug interactions, malabsorption, and potential toxicities including the immune reconstitution inflammatory syndrome.

CONCLUSION

Of all areas of HIV care, the management of opportunistic respiratory infections has been and remains among the most challenging. The evolution of research and care towards a multidisciplinary approach to co-infection constitutes a small but important step forward, a step which has fortunately been accompanied by a simultaneous giant leap forward in acknowledging the global nature of the HIV epidemic. For both clinicians and researchers, there remains much work to do.

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References

1. Kohli R, Lo Y, Homel P, et al. Bacterial pneumonia, HIV therapy, and disease progression among HIV-infected women in the HIV epidemiologic research (HER) study. Clin Infect Dis. 2006; 43:90–8. *The rate of bacterial pneumonia in HIV-infected women remains extremely high despite the introduction of ART. [PubMed: 16758423]
2. Penaranda M, Falco V, Payeras A, et al. Effectiveness of polysaccharide pneumococcal vaccine in HIV-infected patients: a case-control study. Clin Infect Dis. 2007; 45:e82–7. *A case control study that identified ART and the polysaccharide pneumococcal vaccine as independently lowering the risk of pneumococcal infection, even in patients with a CD4 count less than 200 cells/μL. [PubMed: 17806042]
3. Flannery B, Heffernan RT, Harrison LH, et al. Changes in invasive Pneumococcal disease among HIV-infected adults living in the era of childhood pneumococcal immunization. Ann Intern Med. 2006; 144:1–9. *A cohort study suggesting that the introduction of the pediatric pneumococccal conjugate vaccine has decreased the rate of invasive pneumococcal disease in HIV-infected adults. [PubMed: 16389249]
4. Klein MB, Lu Y, DelBalso L, et al. Influenzavirus infection is a primary cause of febrile respiratory illness in HIV-infected adults, despite vaccination. Clin Infect Dis. 2007; 45:234–40. *Influenza is a common cause of febrile respiratory symptoms in HIV-infected patients on ART presenting to an outpatient clinic for care despite high rates of prior influenza vaccination. [PubMed: 17578785]
5. Getahun H, Harrington M, O'Brien R, et al. Diagnosis of smear-negative pulmonary tuberculosis in people with HIV infection or AIDS in resource-constrained settings: informing urgent policy changes. Lancet. 2007; 369:2042–9. *A compelling argument for modification of national TB evaluation algorithms. [PubMed: 17574096]
6. Dowdy DW, Chaisson RE, Moulton LH, et al. The potential impact of enhanced diagnostic techniques for tuberculosis driven by HIV: a mathematical model. AIDS. 2006; 20:751–62. *A sophisticated mathematical analysis of the impact of a variety of diagnostic and public health measures on TB-control in areas of high HIV prevalence is presented. [PubMed: 16514306]
7. Mazurek GH, Jereb J, Lobue P, et al. Guidelines for using the QuantiFERON-TB Gold test for detecting Mycobacterium tuberculosis infection, United States. MMWR Recomm Rep. 2005; 54:49–55. [PubMed: 16357824]
8. Luetkemeyer AF, Charlebois ED, Flores LL, et al. Comparison of an interferon-gamma release assay with tuberculin skin testing in HIV-infected individuals. Am J Respir Crit Care Med. 2007; 175:737–42. *The first large comparative study of TIGRA and TST performance in HIV-infected patients raises difficult questions about how to interpret discordant results between the two tests. [PubMed: 17218620]
9. Jafari C, Ernst M, Kalsdorf B, et al. Rapid diagnosis of smear-negative tuberculosis by bronchoalveolar lavage enzyme-linked immunospot. Am J Respir Crit Care Med. 2006; 174:1048–54. [PubMed: 16858013]
10. Wood R, Middelkoop K, Myer L, et al. Undiagnosed tuberculosis in a community with high HIV prevalence: implications for tuberculosis control. Am J Respir Crit Care Med. 2007; 175:87–93. [PubMed: 16973982]

11. Golub JE, Saraceni V, Cavalcante SC, et al. The impact of antiretroviral therapy and isoniazid preventive therapy on tuberculosis incidence in HIV-infected patients in Rio de Janeiro, Brazil. AIDS. 2007; 21:1441–8. *In spite of its retrospective design, this study provides a thought-provoking examination of the efficacy of IPT in HIV-infected patients. [PubMed: 17589190]
12. Elzi L, Schlegel M, Weber R, et al. Reducing tuberculosis incidence by tuberculin skin testing, preventive treatment, and antiretroviral therapy in an area of low tuberculosis transmission. Clin Infect Dis. 2007; 44:94–102. [PubMed: 17143823]
13. Cohen T, Lipsitch M, Walensky RP, et al. Beneficial and perverse effects of isoniazid preventive therapy for latent tuberculosis infection in HIV-tuberculosis coinfected populations. Proc Natl Acad Sci U S A. 2006; 103:7042–7. *An important discussion of the pros and cons of IPT for LTBI in HIV-infected persons. [PubMed: 16632605]
14. Gandhi NR, Moll A, Sturm AW, et al. Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa. Lancet. 2006; 368:1575–80. **All HIV- and TB- specialists should be familiar with the specter of highly-transmissable XDR TB described in this article, which may serve as a sentinel warning of a new, enormous challenge for TB control. [PubMed: 17084757]
15. Moore DA, Evans CA, Gilman RH, et al. Microscopic-observation drug-susceptibility assay for the diagnosis of TB. N Engl J Med. 2006; 355:1539–50. **The MODS assay is a landmark development in the quest for TB diagnostics for the developing world. [PubMed: 17035648]
16. Nahid P, Gonzalez LC, Rudoy I, et al. Treatment outcomes of patients with HIV and tuberculosis. Am J Respir Crit Care Med. 2007; 175:1199–206. *In an era in which treatment-shortening is in vogue, this paper explores the possibility that a different approach may be necessary in HIV-infected patients. [PubMed: 17290042]
17. Friedland G, Khoo S, Jack C, et al. Administration of efavirenz (600 mg/day) with rifampicin results in highly variable levels but excellent clinical outcomes in patients treated for tuberculosis and HIV. J Antimicrob Chemother. 2006; 58:1299–302. [PubMed: 17032686]
18. Breen RA, Miller RF, Gorsuch T, et al. Virological response to highly active antiretroviral therapy is unaffected by antituberculosis therapy. J Infect Dis. 2006; 193:1437–40. [PubMed: 16619192]
19. Schiffer JT, Sterling TR. Timing of antiretroviral therapy initiation in tuberculosis patients with AIDS: a decision analysis. J Acquir Immune Defic Syndr. 2007; 44:229–34. *In a hypothesis-generating study, the authors find that the consequences of delaying ART in HIV-TB co-infection may outweigh the benefits. [PubMed: 17159657]
20. Bourgarit A, Carcelain G, Martinez V, et al. Explosion of tuberculin-specific Th1-responses induces immune restoration syndrome in tuberculosis and HIV co-infected patients. AIDS. 2006; 20:F1–7. [PubMed: 16511406]
21. Lawn SD, Myer L, Bekker LG, et al. Tuberculosis-associated immune reconstitution disease: incidence, risk factors and impact in an antiretroviral treatment service in South Africa. AIDS. 2007; 21:335–41. *A postulated mechanism for IRIS raises the question: can a diagnostic test for IRIS be far behind? [PubMed: 17255740]
22. Friedland G, Churchyard GJ, Nardell E. Tuberculosis and HIV coinfection: current state of knowledge and research priorities. J Infect Dis. 2007; 196(Suppl 1):S1–3. **The conveners of an expert symposium on HIV-TB co-infection introduce an excellent supplemental *JID* issue, which provides current overviews of the most important issues in the field. [PubMed: 17624818]
23. Huang L, Morris A, Limper AH, et al. An Official ATS Workshop Summary: Recent advances and future directions in pneumocystis pneumonia (PCP). Proc Am Thorac Soc. 2006; 3:655–64. **A concise overview of recent advances in *Pneumocystis* pneumonia. [PubMed: 17065370]
24. Aderaye G, Bruchfeld J, Aseffa G, et al. Pneumocystis jiroveci pneumonia and other pulmonary infections in TB smear-negative HIV-positive patients with atypical chest X-ray in Ethiopia. Scand J Infect Dis. 2007:1–9. *Highlights the frequency of bacterial pneumonia and PCP in HIV-infected patients in Africa who are sputum smear negative for acid fast bacilli.
25. Wong ML, Back P, Candy G, et al. Pneumocystis jirovecii pneumonia in African miners at autopsy. Int J Tuberc Lung Dis. 2006; 10:756–60. *An extremely comprehensive autopsy study of African miners, documenting a high rate of unsuspected PCP and presumably HIV prior to death. [PubMed: 16848337]

26. D'Egidio GE, Kravcik S, Cooper CL, et al. Pneumocystis jiroveci pneumonia prophylaxis is not required with a CD4+ T-cell count < 200 cells/mul when viral replication is suppressed. AIDS. 2007; 21:1711–5. *Suggests that PCP prophylaxis can be discontinued in HIV-infected patients who are on ART and have a sustained undetectable viral load, even if the CD4 count remains under 200 cells/μL. [PubMed: 17690568]
27. Huggett JF, Taylor MS, Kocjan G, et al. Development and evaluation of a real-time PCR assay for detection of Pneumocystis jirovecii DNA in bronchoalveolar lavage fluid of HIV-infected patients. Thorax. 2007 *Describes a novel means of PCP diagnosis based on a PCR assay utilizing primers to the heat-shock protein 70 gene.
28. Morris A, Kingsley LA, Groner G, et al. Prevalence and clinical predictors of Pneumocystis colonization among HIV-infected men. Aids. 2004; 18:793–8. [PubMed: 15075515]
29. Morris A, Sciurba FC, Lebedeva IP, et al. Association of chronic obstructive pulmonary disease severity and Pneumocystis colonization. Am J Respir Crit Care Med. 2004; 170:408–13. [PubMed: 15117741]
30. Norris KA, Morris A, Patil S, et al. Pneumocystis colonization, airway inflammation, and pulmonary function decline in acquired immunodeficiency syndrome. Immunol Res. 2006; 36:175–87. *An excellent review describing the association between *Pneumocystis* colonization and obstructive lung disease (OLD). [PubMed: 17337778]
31. Morris A, Wachter RM, Luce J, et al. Improved survival with highly active antiretroviral therapy in HIV-infected patients with severe Pneumocystis carinii pneumonia. Aids. 2003; 17:73–80. [PubMed: 12478071]
32. Miller RF, Allen E, Copas A, et al. Improved survival for HIV infected patients with severe Pneumocystis jirovecii pneumonia is independent of highly active antiretroviral therapy. Thorax. 2006; 61:716–21. **Shows that mortality from severe PCP requiring ICU care has decreased over time but is independent of ART, suggesting that other factors such as low tidal volume ventilation for acute respiratory distress syndrome and fluid conservative management may be responsible. [PubMed: 16601092]
33. Morris A, Masur H, Huang L. Current issues in critical care of the human immunodeficiency virus-infected patient. Crit Care Med. 2006; 34:42–9. *An overview of the changing epidemiology of HIV-infected patients in the ICU during the ART era. [PubMed: 16374154]
34. Huang L, Quartin A, Jones D, et al. Intensive care of patients with HIV infection. N Engl J Med. 2006; 355:173–81. **A review focusing on the use of ART in the ICU. The article includes a useful clinical algorithm that provides a framework for making decisions regarding use of ART in the ICU. [PubMed: 16837681]