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Update on Opportunistic Infections in the Era of Effective Antiretroviral Therapy

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Introduction

Despite efforts to diagnose and treat HIV infection before patients develop advanced disease, opportunistic infections (OIs) continue to occur in the era of effective antiretroviral therapy (ART), particularly in those who have not yet been diagnosed with HIV and in those who are not receiving therapy. In the US, approximately 1/3 of patients have a CD4 cell count below 200/mm³ at the time of HIV diagnosis, placing them at risk for OIs.¹

Although most OIs occur in patients with CD4 cell counts below 200/mm³, a small residual risk remains even in those with higher counts. A recent analysis of patients with CD4 cell counts >200/mm³ found that esophageal candidiasis, Kaposi Sarcoma and pulmonary tuberculosis were the most common opportunistic conditions in this population.² Factors associated with increased risk of AIDS-defining illness (ADI) in patients with a CD4 cell count >500/mm³ included injection drug use, older age and having a HIV RNA >10,000 copies/mL.² The incidence of OIs appears to level off at a CD4 cell count of 750/mm³, suggesting immune reconstitution is near complete at this level.²

This review will focus on tuberculosis (TB) and cryptococcal infections, the most common OIs in patients living with HIV around the world, as well as on new developments in Progressive Multifocal Leukoencephalopathy and *Pneumocystis* pneumonia. In the sections on these conditions, we provide updates on diagnosis, treatment and complications, as well as information on when to start ART. We conclude with a discussion of new data on two vaccine-preventable OIs, human papillomavirus and varicella-zoster virus. For information on other OIs, please consult the recently updated U.S. Department of Health and Human

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Services (DHHS) Guidelines for the Prevention and Treatment of Opportunistic Infection in HIV-Infected Adults and Adolescents, which provides a comprehensive review.³

Tuberculosis in HIV-infected Patients

Epidemiology

Since the widespread use of ART and intensive TB control efforts in the 1990s, TB incidence among HIV-infected individuals in the US has declined; in fact, the decrease outpaces those seen in HIV-uninfected individuals.^{4,5} In 2012, there were 9,945 cases of tuberculosis in the US, of whom 625 (7%) were coinfecting with HIV.^{4,5}

Latent TB Infection (LTBI)

Patients should be tested for LTBI at the time of HIV diagnosis; if negative, the test should be repeated if the patient is exposed to TB.³ LTBI in HIV-infected individuals is defined as a tuberculin skin test (TST) with >5 mm of induration without clinical or radiographic evidence of active disease. However, a positive TST results is not completely specific for TB: Patients who are infected with some non-tuberculous mycobacteria or who have recently received BCG vaccination may have a false-positive result. A false-negative TST may occur in patients with severe immunodeficiency; for that reason, if testing is negative when the patient's CD4 cell count is $<200/\text{mm}^3$, the test should be repeated after the patient receives ART and achieves immune reconstitution. Finally, the TST has several logistic disadvantages, including the need for a return visit for the test to be read and variability in how it is placed and interpreted.

Interferon-gamma release assays (IGRAs), a blood test, require only a single visit and have higher specificity than the TST for diagnosis of LTBI. In HIV-uninfected individuals, there is good concordance (89%) between an IGRA and TST.⁶ However, in HIV-infected individuals in low TB prevalence areas, the concordance between TST and IGRA results is not as good.⁷ In addition, those with a CD4 cell count $<200/\text{mm}^3$ are more likely to have indeterminate results.⁷ Nevertheless, both the TST and IGRA are considered appropriate tests for diagnosis of LTBI in HIV-infected patients.⁸ Of note, although a recent study found that an IGRA had good sensitivity for active TB in HIV-infected patients^{7,8}, other studies have found that the TST and IGRAs may be negative in patients with TB; therefore, a negative result does not exclude active infection.⁹

Treatment of LTBI

Isoniazid (INH) daily for 9 months has been standard therapy for patients with LTBI for many years.¹⁰ The efficacy of INH monotherapy is 69% to 93%;¹¹ however, completion rates are low (30% to 64%).^{12,13} Recently, a study of once-weekly INH and rifapentine by directly observed therapy for 3 months was found to be as effective as 9 months of INH for preventing active TB and had a significantly higher completion rate (82% vs. 69%).¹⁴ However, this regimen is not recommended for HIV-infected individuals who are receiving ART because of the potential for drug interactions between rifapentine and ART.³

Diagnosis of Active Tuberculosis

Typically, tuberculosis is diagnosed by detecting *Mycobacterium tuberculosis* in smear or culture from sputum or other samples (e.g. in highly immunosuppressed patients, blood cultures may grow the organism). In patients with suspected pulmonary TB, sputum smears for acid-fast bacilli (AFB) should be performed, along with culture, which has higher sensitivity than smear. Culture of three sputum specimens should be considered because the 2nd and 3rd cultures increase the incremental AFB yield (by 17% and 10%, respectively).¹⁵ In immunosuppressed patients, extra-pulmonary TB is frequent; in this setting the sputum AFB smear may be negative. Fortunately, new diagnostic tests have been developed that are improving the ability to diagnose TB.

GeneXpert

Recent development of the GeneXpert MTB/RIF brings rapid point-of-care diagnostics to the field of tuberculosis. This automated nucleic-acid amplification test uses real-time PCR to amplify a TB-specific portion of the *rpoB* gene which is then probed for mutations within the rifampin resistance-determining region. This assay can provide results in a few hours compared to up to 6 weeks for mycobacterial culture. In a study of patients with suspected pulmonary TB conducted in Peru, Azerbaijan, South Africa, and India, the sensitivity of GeneXpert in smear-positive disease was 98%.¹⁶ Among HIV-infected patients with pulmonary TB, the sensitivity was 94%. In smear-negative disease, the sensitivity for one GeneXpert test was 72.5%, for two tests was 85%, and for three tests was 90%.¹⁶ The test also had high specificity (99%). As compared to phenotypic methods, the GeneXpert test correctly identified 98% of rifampin-resistant and rifampin-sensitive isolates.¹⁶ (Other nucleic acid-based genotypic methods can detect both isoniazid and rifampin resistance).¹⁷

The GeneXpert test has now been tested in a variety of settings, and on patients with pulmonary and extra-pulmonary TB. A recent meta-analysis that analyzed 10,224 suspected specimens estimated a sensitivity of 90% (lower in smear-negative samples than in smear-positive sputa) and a specificity of 98% in diagnosing pulmonary tuberculosis.¹⁸ The sensitivity for detecting rifampin resistance was 94% and specificity was 97%. For extra-pulmonary tuberculosis the sensitivity was 80% and specificity was 86%.¹⁸

Currently, GeneXpert is approved for use on sputum only. Several studies evaluating the GeneXpert platform on extrapulmonary samples found variability in its sensitivity and specificity depending on the tissue and sample site.^{19–22} Overall, the performance of the GeneXpert for extrapulmonary TB appears to improve with decreasing CD4 cell count.¹⁹ Additional studies will be required to determine its effectiveness in diagnosing TB when used on samples other than sputum.

Lipopolysaccharide Antigen Lipoarabinomannan (LAM)

The detection of the *Mycobacterium tuberculosis* cell wall lipopolysaccharide antigen lipoarabinomannan (LAM) in urine has been developed as a test to diagnose tuberculosis without regard to the specific anatomical site of infection. In a study of 199 tuberculosis patients in South Africa, 16% of patients tested positive for LAM by ELISA.²³ The

sensitivity was highest in those with CD4 cell count $< 50/\text{mm}^3$ (69%) and declined with increasing CD4 counts: 43% in those with CD4 counts between 50–99, 32% in those between 100–199 and only 15% in those >200 . Recently a low-cost point-of-care lateral-flow assay using a urine dipstick has been developed to detect LAM.^{24,25}

Treatment of TB in HIV-infected Patients

HIV-infected patients with TB should receive the same treatment as HIV-negative individuals. Particular attention should be given to drug interactions between anti-tuberculous therapy and specific antiretroviral medications (Table 2). Daily therapy (5–7 days/week), rather than intermittent dosing, is recommended during the intensive phase. During the continuation phase, daily- or thrice-weekly dosing should be given; less frequent dosing has been associated with higher rates of treatment failure or relapse, perhaps because of malabsorption in HIV/TB coinfecting patients with low CD4 cell counts.

When to Start Antiretroviral Therapy in an HIV-infected Patient with Tuberculosis

Sequential treatment, in which a course of therapy for tuberculosis is completed followed by ART initiation, has been shown to increase mortality in those with drug-sensitive or multidrug-resistant TB and is not recommended.^{26,27} Several studies have demonstrated that integrated-treatment of HIV and TB improves survival, prevents other OIs, and may improve TB treatment outcomes.^{26–29}

In the SAPIT study, 642 HIV-infected South African adults with CD4 cell counts $< 500/\text{mm}^3$ and smear-positive TB were randomized to start ART within 4 weeks after initiating TB therapy (early integrated-therapy), within 4 weeks after completion of the intensive phase of TB treatment (late integrated-therapy), or after TB treatment was completed (sequential-therapy).²⁹ In all CD4 cell count strata, mortality was significantly higher in the sequential-therapy group than in the combined integrated-therapy groups.²⁶ The benefit of early integrated-therapy was greatest in those with CD4 cell counts $< 50/\text{mm}^3$.²⁹ Patients with higher CD4 cell counts who received late integrated-therapy had a lower incidence of immune reconstitution inflammatory syndrome (IRIS) and adverse events requiring ART change compared with those who received early integrated-therapy.²⁹

The CAMELIA study randomized 661 HIV-infected Cambodian adults with TB and a median CD4 cell count of $25/\text{mm}^3$ to start ART treatment at 2 or 8 weeks after initiation of TB therapy.³⁰ Although the incidence of IRIS was 2.5-fold higher in the 2-week ART group, this was outweighed by the mortality benefit: Risk of death was significantly lower in the 2-week group (18%) than in the 8-week group (27%).

In the STRIDE study (ACTG A5221), 809 HIV-infected patients with suspected TB and a CD4 cell count of $< 250/\text{mm}^3$ were randomized to earlier-ART (within 2 weeks of TB therapy initiation) or to later-ART (between 8–12 weeks after starting TB therapy).²⁸ The earlier-ART group had a lower rate of AIDS-defining illness (ADI) or death than the later-ART group (12.9% vs. 16.1%), but the difference was not significant. In patients with a CD4 cell count $< 50/\text{mm}^3$, however, there was a significant decrease in new ADI or death in the earlier-ART (15.5%) compared to the later-ART group (26.6%). TB-IRIS occurred in 5% of patients in the earlier-ART group and in 11% of those in the later-ART group.³¹

Based on these findings, the WHO recommends starting ART in all people with HIV and active TB regardless of CD4 cell count, and that TB treatment should be started first, followed by ART within the first 8 weeks of TB therapy.³² The DHHS guidelines recommend ART for all HIV-infected individuals with TB. ART should be initiated within 2 weeks of TB therapy if the CD4 count is <50 cells/mm³ and by 8–12 weeks if the CD4 cell count is higher (see Table 1).³

TB Meningitis (TBM)

When ART should be started in patients with TBM is less certain. In a randomized study of 253 HIV-infected patients with TBM in Vietnam, there was no mortality benefit in patients who initiated ART immediately compared with those who deferred ART for 2 months after starting tuberculosis therapy. There were more severe adverse events in the immediate group than in the deferred group. The overall mortality was extremely high: 60% in the immediate ART group and 56% in deferred ART group.³³ This study highlights the high mortality and severe complications associated with TBM.

Antiretroviral Medication Choice in Patients with HIV/TB

Significant drug-drug interactions exist between TB therapy and several antiretroviral medications (Table 2). Because rifampin markedly decreases levels of HIV protease inhibitors, non-nucleoside reverse transcriptase inhibitors, such as efavirenz, are often used in HIV-TB coinfecting patients instead. Efavirenz-based regimens have been found to have lower rates of virologic failure than nevirapine-based ART in HIV-TB coinfecting individuals.^{34,35} In a study conducted in Thailand, there was no difference in virologic or immunologic outcomes with efavirenz 600 mg daily compared to 800 mg daily in HIV-TB coinfecting individuals, supporting standard dosing of this drug in this population.³⁶ A recent pharmacokinetic evaluation of the STRIDE study found that co-administration of efavirenz and rifampin was associated with a trend towards higher, rather than lower, efavirenz C_{min} compared to efavirenz alone.³⁷ Those weighing ≥ 60 kg had lower efavirenz C_{min} than those < 60 kg, but did not have lower viral suppression rates.

When an efavirenz-based regimen cannot be used, an HIV protease inhibitor-based regimen may be given with rifabutin- rather than rifampin-based TB therapy. (Rifabutin doses should be lowered because PIs increase its level.) To overcome the PI-lowering effect of rifampin, high-dose ritonavir (so-called “super-boosting”) with lopinavir has been studied; although this regimen has favorable pharmacokinetic data when co-administered with rifampin, there have been unacceptably high rates of toxicity, intolerance, and treatment discontinuation.^{38,39}

Levels of the HIV integrase inhibitor raltegravir are lowered when co-administered with rifampin. Doubling the standard raltegravir dose to 800 mg twice daily compensates for the effect of rifampin on raltegravir exposure but still results in low raltegravir trough concentrations.⁴⁰ In a randomized phase 2 trial of HIV-TB coinfecting patients on rifampin-based therapy, standard dose raltegravir (400 mg twice daily) compared favorably to efavirenz and double-dose raltegravir (800 mg twice daily) (reference below), but a larger phase 3 trial is needed to confirm these results.⁴¹ In healthy, HIV-negative volunteers, co-

administration of rifabutin did not have a clinically meaningful effect on raltegravir pharmacokinetics.⁴² Twice-daily dolutegravir with rifampin or once-daily dolutegravir with rifabutin appear to provide acceptable drug levels.⁴³ Although promising, more data is needed on the efficacy and toxicity of co-administration of HIV integrase inhibitors with TB therapy

Cryptococcus

Epidemiology

The incidence of cryptococcal meningitis (CM) has decreased substantially in resource-rich settings during the era of effective ART. However, the global burden of cryptococcal infection is still substantial: in 2006, the number of cases was estimated to be 960,000 and the number of deaths due to CM was about 625,000.⁴⁴ This infection typically occurs in those with a CD4 cell count $<100/\text{mm}^3$.

Diagnosis

In the US, cryptococcal infection is usually diagnosed by serum or CSF cryptococcal antigen (CrAg) testing or by culture. Other testing methods, including India ink staining of CSF, are used in other parts of the world. In HIV-infected patients, the serum CrAg is usually positive in meningeal or non-meningeal disease. Assays for detection of CrAg include latex agglutination (LA), enzyme immunoassay (EIA) or lateral flow assay (LFA). LA and EIA require laboratory expertise and infrastructure,⁴⁵ which are frequently not available in resource-limited settings.

Cryptococcal Antigen Lateral Flow Assay (LFA)

The LFA is a dipstick immunochromatographic assay in which gold-conjugated, anti-*Cryptococcus* antibodies deposited on the test strip membrane are used to detect CrAg in serum, plasma, CSF or urine; if antigen is detected, a visible line appears. This easy, inexpensive, point-of-care test can be used for rapid diagnosis of cryptococcal infection without the need for significant laboratory infrastructure. A recent evaluation in 832 African patients with suspected meningitis reported a sensitivity and specificity for the LFA in CSF samples of 99.3% and 99.1% respectively.⁴⁶ Notably, the LFA outperformed latex agglutination assays in terms of accuracy. In a recent study in 112 Ugandan patients with suspected meningitis, the CSF LFA titer at time of diagnosis correlated with fungal burden and mortality.⁴⁷ Near-perfect performance of LFA in patients with confirmed meningitis has also been demonstrated in plasma, serum, and urine specimens, with sensitivities $>95\%$.^{46,48} However, more information is needed on the performance of the LFA in peripheral specimens in patients without meningitis. A study evaluating LFA accuracy among hospitalized patients in Thailand with respiratory illness found, as compared to serum EIA, the sensitivity of LFA was 96% in serum and 70% in urine. Because of its ease of use and accuracy, the LFA may be used as a screening strategy for cryptococcal infection in patients with advanced HIV infection in areas of the world and populations where there is high prevalence of cryptococcal antigenemia, such as parts of sub-Saharan Africa.⁴⁹

Treatment of Cryptococcal Meningitis: The Induction Phase

There have been many important clinical trials evaluating different treatment strategies for HIV-infected patients with cryptococcal meningitis.^{49–51} In a recently published trial of induction therapy, 299 HIV-infected patients with CM were randomized to receive amphotericin B alone for 4 weeks, amphotericin B plus flucytosine for 2 weeks, or amphotericin B plus fluconazole 400 mg twice daily for 2 weeks, all followed by fluconazole 400 mg daily for 6–8 weeks.⁵² The amphotericin B plus flucytosine group had a significantly lower mortality by day 70 than the amphotericin B alone group (hazard ratio, HR, 0.61); the amphotericin plus fluconazole group also had a lower mortality rate than the monotherapy group, but the difference was not significant (HR for death, 0.71, $p=0.13$).

Historically, amphotericin B deoxycholate was the formulation used to treat CM; however, where available, lipid formulations of amphotericin B are now preferred because of improved tolerance.⁵³ Current US recommendations for the induction treatment of CM is with liposomal amphotericin B at 3–4 mg/kg/day in combination with flucytosine 100mg/kg divided in 4 equal doses daily for at least 2 weeks.³

Consolidation and Maintenance Therapy

After at least two weeks of induction therapy, if the patient has clinically responded and has a negative CSF culture, the patient may be switched to consolidation therapy with fluconazole 400 mg daily for at least 8 weeks. The fluconazole dose may then be reduced to 200 mg daily; this maintenance phase of therapy should continue for at least one year. Therapy may be stopped in patients who have received at least 12 months of fluconazole maintenance therapy, who have CD4 cell counts $\geq 100/\text{mm}^3$, and who have undetectable HIV RNA for 3 months on ART.³

When to Start Antiretroviral Therapy

Several studies have examined the optimal time to initiate ART in patients with CM. ACTG 5164, which randomized HIV-infected patients with acute OIs to receive early ART (within 14 days of OI diagnosis) or deferred ART (after OI therapy was completed) found that early ART improved outcomes;⁵⁴ however, only 35 subjects in this study had cryptococcal infection. A study from Zimbabwe that randomized 54 HIV-infected subjects with CM to receive early ART initiation (within 72 hours of CM diagnosis) or delayed ART initiation (after 10 weeks of treatment with fluconazole alone), found a nearly 3 times higher risk of mortality in the early ART arm.⁵⁵ Several features of this study limit its generalizability to resource-rich settings, including its use of fluconazole monotherapy and the inability to treat elevated intracranial pressure (ICP) with serial lumbar punctures; nevertheless, the trial highlighted the potential danger of early ART in patients with CM.

In the Cryptococcal Optimal ART Timing (COAT) study, HIV-infected patients who received induction therapy with amphotericin B plus fluconazole 800 mg daily were randomized to initiate early ART (within 48 hours of study entry, which was after 7–11 days of induction treatment) or deferred ART (4 weeks after randomization, approximately 5 weeks after initiation of antifungal therapy).⁵⁶ A Safety Monitoring Board stopped the study due to increased mortality in the early treatment group (40/88 [45%] versus 27/89 [30%],

HR=1.7; P=0.03). The benefit of deferring ART was particularly evident in patients with CSF white blood cell count <5 cells/mm³, altered mental status or sepsis. Based on findings from this study, the optimal time to start ART may be approximately 5 weeks after initiation of anti-fungal therapy (Table 1). In addition, effective management of increased ICP and complications, such as cryptococcal IRIS, are critical to achieving a successful outcome.

Cryptococcal IRIS

Cryptococcal IRIS presents as worsening clinical disease or new onset of symptoms of CM after initiation of ART.⁵⁷ Discerning risk factors for cryptococcal IRIS has been complicated by various reports with conflicting results.^{58–60} Some risk factors have included being ART-naïve, having higher HIV RNA levels, persistent CSF fungal culture growth, decreased CSF protein and having lower CNS inflammation at the time of CM diagnosis.^{59,61} There is limited evidence to guide treatment of cryptococcal IRIS. Recent guidelines suggest continuing antifungal therapy and ART, and aggressive management of increased ICP, if present; some experts also recommend a brief steroid course.^{3,57}

Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is caused by JC virus infection of oligodendrocytes in the central nervous system, leading to focal demyelination. In the era of effective ART, the incidence of PML in HIV-infected individuals has decreased significantly.⁶² Median survival has also improved but mortality remains high and those who survive frequently suffer permanent neurological deficits.⁶³ Although PML usually affects HIV-infected patients with low CD4 cell counts, there are reports of PML occurring in individuals with CD4 cell counts >100/mm³ as well as in HIV-uninfected patients receiving immunomodulatory antibodies as treatment for cancer or autoimmune disorders.^{64,65}

Treatment of PML

Currently, there is no effective antiviral agent against JC virus. In HIV-infected patients, treatment of PML consists of ART to reverse immunosuppression and restore anti-JC virus immunity. Although it has been proposed that ART with higher CNS penetration may prevent HIV-associated CNS diseases, such as PML, a cohort study of over 22,000 HIV-infected individuals found that these CNS events were not significantly associated with the CNS penetration effectiveness (CPE) score of the antiretroviral regimen.⁶⁶ In addition, in the current era of effective ART, plasma HIV RNA correlates with clinical outcomes in patients with neurologic AIDS-defining events, such as PML, whereas CPE does not.⁶³ In a patient with PML, a regimen should be chosen that has the highest likelihood of systemic suppression of HIV replication and immune restoration.

Several drugs with promising *in vitro* anti-JC activity have not been found to have clinical efficacy in patients with PML. Trials with cytarabine,⁶⁷ cidofovir,⁶⁸ and mefloquine⁶⁹ have been unsuccessful. It has recently been found that the serotonin receptor 5HT_{2a} can serve as a receptor for the JC virus; therefore serotonin receptor inhibitors, such as mirtazapine, have been proposed as treatment for PML.⁷⁰ Several case reports suggested clinical benefit with

mirtazapine in HIV-infected and non-infected individuals with PML; however, there have been no published randomized studies to date.^{71–73}

PML-IRIS

Both unmasking of previously unrecognized PML and paradoxical worsening in patients with known PML have been observed in patients after initiation of ART. Although steroids are sometimes used to treat PML-IRIS, their role is still controversial.^{64,74} One of the postulated mechanisms of PML-IRIS is that CCR5+ immune cells mediate this complication. For this reason, maraviroc, a CCR-5 antagonist, was given to a HIV-negative woman with multiple sclerosis who was at high risk for PML-IRIS after receiving natalizumab.⁷⁵ In this case report, maraviroc seemed to initially prevent PML-IRIS and subsequently improve IRIS once it occurred. Additional studies of maraviroc in patients with PML are being planned.

Pneumocystis Pneumonia

Pneumocystis pneumonia (PCP) is caused by the fungus *Pneumocystis jirovecii*. In HIV-infected patients, risk factors for PCP include CD4 cell count <200/mm³, CD4 percentage less than 14%, oral thrush, unintentional weight loss, and high plasma HIV RNA level.^{76,77}

The incidence of PCP has declined significantly as a result of prophylaxis and effective ART.⁷⁸ At this point, PCP in HIV-infected patients is most commonly seen in those who are unaware of their HIV status or not engaged in care. Interestingly, nosocomial outbreaks of *Pneumocystis jirovecii* have been seen among renal transplant patients.⁷⁹ Increasing evidence suggests that aerosolization of the fungus can occur from infected patients and may play a role in nosocomial transmission.⁸⁰

Diagnosis

PCP cannot be cultured routinely; therefore, diagnosis requires detection of the organism by microscopic examination of induced sputum, bronchial alveolar lavage (BAL), or tissue. Examination of induced sputum has variable sensitivity (<50% to >90%).³ BAL has a high sensitivity for PCP; however, it is an invasive procedure with potential morbidity in patients with respiratory compromise. Elevated serum lactate dehydrogenase is a nonspecific marker, which is often elevated in cases of PCP.⁸¹ Serum (1→3)-β-D-glucan (β-glucan), a component of the cell wall of *Pneumocystis jirovecii*, may also be elevated in patients with PCP but there is significant cross reactivity with other fungal diseases.⁸² A recent study evaluated β-glucan testing in 252 HIV-infected individuals with opportunistic infections, of whom 173 (69%) were diagnosed with PCP;⁸³ the overall sensitivity of the test for the diagnosis of PCP was 92% and specificity was 65%. In HIV-infected patients with respiratory symptoms, the test performed better (sensitivity 93%, specificity 75%, positive predictive value 96%, negative predictive value 60%).⁸⁴ In the appropriate clinical setting, β-glucan testing can aid in the diagnosis of PCP.

When to Start ART in a Patient with PCP

ACTG A5164, which evaluated early (within 2 weeks of OI diagnosis) versus deferred ART initiation (after OI therapy was completed) in patients with opportunistic infections found a significant decrease in AIDS progression or death with early ART; the majority of patients in this study had PCP.⁵⁴ Current guidelines recommend starting ART within 2 weeks of diagnosis of PCP (see Table 1).³

Recommendations for PCP Prophylaxis

Indications for initiating PCP prophylaxis, preferred and alternative therapies and indications for stopping primary prophylaxis are summarized in Table 3.

Vaccine-Preventable Opportunistic Infections

Human Papillomavirus

Epidemiology—Infection with oncogenic high-risk human papillomavirus (HPV) types is the major risk factor for the development of cervical cancer in women and anal cancer in both men and women. The oncogenic types include HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59.⁸⁵ HPV 16 and 18 cause approximately 70% of all cervical cancers worldwide. All of the other types individually contribute less than 5% each to cervical cancers.

HPV Vaccine—Currently there are two HPV vaccines licensed in the US: the bivalent vaccine protects against HPV 16 and 18; the quadrivalent vaccine protects against HPV 16 and 18 and the non-oncogenic HPV 6 and 11 (the most common causes of genital warts). Clinical trials have found both vaccines efficacious in preventing cervical pre-cancer in women; the quadrivalent vaccine has also shown efficacy for preventing vaginal and vulvar pre-cancer in women and in preventing anal intraepithelial neoplasia in men who have sex with men (MSM).^{86–88}

The CDC Advisory Committee on Immunization Practices (ACIP) recommends:⁸⁹

- For females, either the bivalent or quadrivalent HPV vaccine at age 11 or 12 years and for those aged 13–26 years if not previously vaccinated
- For males, quadrivalent HPV vaccine at age 11 or 12 years and for those aged 13–21 years if not previously vaccinated. Males aged 22 through 26 years may be vaccinated.
- MSM and immunocompromised persons (including HIV-infected males and females) should be vaccinated through age 26 years if not previously vaccinated.

The quadrivalent HPV vaccine is safe and immunogenic in HIV-infected women and men.^{90–92}

Varicella and Zoster Vaccines

Epidemiology—Over 95% of United States-born adults are immune to varicella zoster virus (VZV). Herpes zoster (HZ) results when latent VZV reactivates. In a study among

MSM, the incidence of HZ was much higher in HIV-infected than HIV-negative men (age-adjusted relative risk 16.9).⁹³ Risk factors for HZ in HIV-infected patients include a previous zoster episode and CD4 cell count $<200/\text{mm}^3$.⁹⁴ Use of ART is not necessarily protective against development of HZ, and the risk of HZ may increase soon after ART initiation.^{95,96}

Vaccination in HIV-infected Patients—The live attenuated varicella vaccine is recommended for HIV-infected children with CD4 percentage $>15\%$.^{93,97,98} The 2014 ACIP Guidelines and the 2013 Infectious Diseases Society of America (IDSA)/HIV Medical Association (HIVMA) Primary Care Guidelines for HIV-infected Patients recommend varicella vaccination in HIV-infected/VZV-seronegative adults with CD4 cell counts $>200/\text{mm}^3$.^{89,99}

ACTG A5247 evaluated live attenuated zoster vaccine in HIV-infected adults on ART with CD4 cell count >200 cells/ mm^3 and HIV RNA <50 copies/mL; the vaccine was found to be safe and triggered an antibody response.¹⁰⁰ At the current time, however, ACIP does not recommend zoster vaccine in HIV-infected patients. The IDSA/HIVMA guidelines state that zoster vaccine should be considered in HIV-infected patients 60 years of age or older who have a CD4 cell count $>200/\text{mm}^3$.⁹⁹

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Key Points

- New diagnostic tests are improving the ability to detect tuberculosis, cryptococcal meningitis and *Pneumocystis* pneumonia in HIV-infected patients.
- Randomized trials support early initiation of antiretroviral therapy (ART) in HIV-infected patients with tuberculosis; however, a slight delay in initiation of ART in patients with cryptococcal meningitis may be warranted.
- Although new therapies have been tested in HIV-infected patients with progressive multifocal leukoencephalopathy, ART is still the mainstay of therapy.
- Young HIV-infected males and females should receive the quadrivalent human papillomavirus vaccine.
- Varicella vaccine is recommended for non-immune HIV-infected individuals with CD4 cell count $>200/\text{mm}^3$. Zoster vaccine appears to be safe and immunogenic in HIV-infected patients on ART with high CD4 cell counts.

Table 1When to Start Antiretroviral Therapy (ART) in Patients with Opportunistic Infections (OIs)^{3,54,56}

Opportunistic Infection	When to Start ART
<ul style="list-style-type: none"> • Cryptosporidiosis • Microsporidiosis • Progressive multifocal leukoencephalopathy 	As part of initial therapy for the OI
<ul style="list-style-type: none"> • Pneumocystis pneumonia • Mycobacterium avium-complex • Toxoplasmosis 	Within ~2 weeks of initiating OI treatment
<ul style="list-style-type: none"> • Tuberculosis (TB) 	<ul style="list-style-type: none"> • CD4 cell count < 50/mm³ – within 2 wks after starting TB therapy • CD4 cell count >50/mm³ – within 8 to 12 weeks after starting TB therapy
<ul style="list-style-type: none"> • Cryptococcal Meningitis 	~approximately 5 wk after starting antifungal therapy

Table 2Drug interactions between anti-tubercular and antiretroviral medications³

Anti-TB drug	Antiretroviral drug	Effects and Recommendations
Rifampin	Efavirenz	In patients < 60 kg, lower efavirenz C _{min} when administered with rifampin; no association between higher weight and reduced virologic suppression; no change in dose recommended ³¹
	Elvitegravir/cobicistat/tenofovir/emtricitabine	Cobicistat and elvitegravir level may decrease – co-administration should be avoided
	Etravirine	Etravirine levels may decrease– co-administration should be avoided
	Maraviroc	Maraviroc level decreases -- increase maraviroc to 600 mg twice daily or use alternative
	Nevirapine	Nevirapine level decreases – coadministration should be avoided if possible
	Protease inhibitor (with or without ritonavir)	PI level significantly decreases – co-administration should be avoided
	Raltegravir	Raltegravir level decreases – label advises increase in dose to 800 mg twice daily; monitor efficacy closely or switch rifampin to rifabutin; see text for more information regarding raltegravir dosing in this setting
	Rilpivirine	Rilpivirine level decreases – co-administration should be avoided
	Zidovudine	Zidovudine level decreases - No dosage adjustments recommended; monitor efficacy
Rifabutin	Efavirenz	Rifabutin level decreases; efavirenz exposure unchanged – Increase rifabutin to 450–600 mg daily
	Elvitegravir/cobicistat/tenofovir/emtricitabine	Rifabutin metabolite level markedly increases; elvitegravir level decreases -- co-administration should be avoided
	Etravirine	Etravirine and rifabutin levels decrease – no dosage adjustment recommended
	Maraviroc	May decrease maraviroc levels – if using with strong CYP3A4 inhibitor, maraviroc dosing should be 150 mg twice daily; if not, maraviroc should be 300 mg twice daily
	Nevirapine	Rifabutin level increases; nevirapine level decreases – no dose adjustments recommended
	Protease inhibitor (with ritonavir boosting)	Rifabutin level significantly increases – use rifabutin dose 150 daily or 300 mg three times per week; consider monitoring levels and adjusting dose accordingly
	Rilpivirine	Rilpivirine level decreases – co-administration should be avoided

Table 3**PCP Prophylaxis³**

<p><u>Indications for Initiating Primary Prophylaxis:</u></p> <ul style="list-style-type: none"> • CD4 cell count <200/mm³ • Oropharyngeal candidiasis • CD4 cell percentage <14% • History of AIDS-defining illness • CD4 cell count >200 but <250/mm³ if CD4 cell count monitoring not feasible <p><u>Preferred Prophylaxis Therapy:</u></p> <ul style="list-style-type: none"> • TMP-SMX, 1 DS PO daily • TMP-SMX, 1 SS PO daily <p><u>Selected Alternative Therapies:</u></p> <ul style="list-style-type: none"> • TMP-SMX 1 DS PO three times a week • Dapsone 100 mg PO daily • Atovaquone 1500 mg PO daily with food <p><u>Indication for Discontinuing Primary Prophylaxis:</u></p> <ul style="list-style-type: none"> • CD4 cell count increased from <200/mm³ to ≥200/mm³ for at least 3 months in response to ART
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