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Announcements

Continuing Medical Education Credit
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The following article in this issue is associated with CME credit:

Instructions
This Continuing Medical Education (CME) activity provides a review of data regarding the management of patients with tuberculosis and HIV coinfection. To complete the activity, the learner is instructed to:

- Read the article
- Review a selection of the references
- Reflect on how the information might be applied to the clinical practice
- Take the posttest
- Complete the CME claim form and send it to the IAS–USA office.

Objectives
Upon completion of this activity, learners will be able to describe results of recent research and the potential clinical implications for their HIV-infected patients on the management of tuberculosis coinfection.

Accreditation Statement
The International AIDS Society–USA is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

The International AIDS Society–USA designates this activity for a maximum of 1.5AMA PRA Category 1 Credits™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Intended Audience
This activity is intended for physicians involved in the care of patients with HIV infection. It is also relevant to nurse practitioners, physician assistants, nurses, and other health professionals who provide care for people with HIV disease.

Author Financial Disclosures
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Posttest Questions
Circle the single best answer to each of the questions below.

1. In 2009, HIV coinfection was present in what proportion of all tuberculosis (TB) cases in the United States?
   A. 5%
   B. 10%
   C. 30%
   D. 50%

2. Interferon gamma release assays (IGRAs) yield positive, negative, or indeterminate test results. Indeterminate test results on IGRA testing:
   A. Occur more frequently with low CD4+ cell counts
   B. Indicate a higher likelihood of TB infection than a negative IGRA result
   C. Are suggestive of previously treated latent TB infection or active TB
   D. Are more common in patients receiving antiretroviral therapy

3. Important drug-drug interactions can occur when patients are treated for both HIV infection and TB. Rifampin is associated with hepatitis and with substantially decreased drug levels of what antiretroviral drug class?
   A. Nucleoside analogue reverse transcriptase inhibitors
   B. Integrase strand transfer inhibitors
   C. Protease inhibitors
   D. Nonnucleoside analogue reverse transcriptase inhibitors

4. Initiation of antiretroviral therapy in TB-infected patients can lead to the development of paradoxical immune reconstitution inflammatory syndrome (IRIS), in which the TB symptoms become worse despite effective TB treatment. In suspected TB IRIS, the appropriate clinical management is:
   A. Discontinue antiretroviral therapy immediately and consider prednisone treatment if IRIS symptoms are severe
   B. Evaluate for TB medication adherence, drug-resistant TB, and other infectious causes, and consider treatment with prednisone for severe symptoms of TB IRIS
   C. Discontinue TB medication immediately and evaluate for drug-resistant TB and for other infectious causes
   D. Order a high-sensitivity C-reactive protein test to help make the diagnosis of IRIS

5. Which of the following treatment options has been demonstrated to decrease the risk of active TB developing in HIV-infected individuals with latent TB infection?
   A. Both isoniazid prevention therapy and antiretroviral therapy
   B. Only isoniazid prevention therapy
   C. Only antiretroviral therapy
   D. No intervention has been demonstrated convincingly to reduce the risk of active TB
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Moving Beyond Interferon Alfa: Investigational Drugs for Hepatitis C Virus Infection

Numerous direct-acting drugs to treat hepatitis C virus (HCV) infection are in development, offering the potential for substantial improvement over current interferon alfa–based therapy and the possibility of effective interferon alfa–sparring regimens in achieving cure of HCV infection. Drugs furthest along in clinical development include HCV nonstructural protein 3 (NS3) protease inhibitors (eg, telaprevir, boceprevir), which have potent anti-HCV activity but low barriers to resistance and considerable likelihood of cross-resistance. Nucleoside analogue nonstructural protein 5B (NS5B) polymerase inhibitors exhibit a high barrier to resistance and cross-HCV genotype and subtype activity. Nonnucleoside analogue polymerase inhibitors have a low barrier to resistance and are characterized by a substantial frequency of preexisting resistance mutations. The initial use of direct-acting drugs will be as add-on treatment to interferon alfa and ribavirin regimens. The success of interferon alfa–sparring regimens will depend on presenting a sufficiently high barrier to resistance with direct-acting drugs and whether the immunomodulatory effects of interferon alfa are needed for cure of HCV infection. This article summarizes a presentation by David L. Wyles, MD, at the International AIDS Society–USA continuing medical education program held in San Francisco in May 2010.

The prevalence of hepatitis C virus (HCV) infection–related cirrhosis and end-stage liver disease (ESLD) is expected to peak around 2020, reflecting the gradual course of progression of HCV disease in individuals infected several decades ago during the peak incidence of infection. The burden of HCV infection in HIV-infected patients is substantial. Reports from the D:A:D (Data Collection on Adverse Events of Anti-HIV Drugs) study in 2006 and 2009 show that liver-related mortality is the most common non–AIDS-related cause of death in HIV-infected patients (D:A:D Study Group and Smith, AIDS, 2010; Weber et al, Arch Intern Med, 2006).

Interferon alfa–based therapy for HCV infection and its delivery to patients leave much to be desired. A majority of HCV-infected patients are ineligible for therapy, and a sizeable proportion of eligible patients refuse treatment. Moreover, a majority of treated patients have no response or discontinue treatment, leaving a very small proportion of the total population of HCV-infected patients with the sustained virologic response (SVR) associated with cure. Limitations of interferon alfa–based therapy include relatively low SVR rates (eg, 40%–45% in HCV genotype 1 infection); markedly lower SVR rates in certain populations (eg, 20% in HIV and HCV coinfection and 20%–25% in blacks even with monoinfection); poor tolerability (including that associated with frequent use of growth factor support), resulting in discontinuation by 10% to 15% of patients for adverse events alone; numerous contraindications; and poor acceptance of therapy.

There is considerable hope that new, direct-acting antiviral drugs and other novel drugs will increase the proportions of HCV-infected patients who can tolerate treatment and patients who achieve cure. Dozens of such drugs are currently in development, notably including nonstructural protein 3 (NS3) protease inhibitors and nucleoside analogue and nonnucleoside analogue nonstructural protein 5B (NS5B) polymerase inhibitors.

Characteristics of Hepatitis C Virus

HCV is a positive-strand RNA virus featuring several nonstructural proteins that are being targeted for drug development. Host cell factors (eg, cyclophilin A) also play key roles in viral replication, providing additional pharmacologic targets. HCV exhibits extremely wide genetic heterogeneity both within and across genotypes, including a 30% to 40% difference in nucleotide sequences between genotypes. Like the replication rate of hepatitis B virus (HBV) (10^{12–13} virions/day) and HIV (10^{10} virions/day), the replication rate of HCV (10^{12} virions/day) is high, producing approximately 10- to 100-fold more virions per day than HIV.

This high replication rate combined with an error-prone viral polymerase and absence of overlapping reading frames drives the genetic diversity of HCV. This diversity includes production of resistant variants of HCV that can elude the inhibitory effects of antiviral drugs that target components of the viral life cycle. For HCV, transcription errors may be multiplied because there are 2 rounds of transcription (from positive to negative strand RNA, and from negative back to positive strand) that utilize the error-prone NS5B polymerase. Unlike for HBV and HIV infections, eradication of HCV does occur. Infected-cell turnover with HCV is not as rapid as that with HIV and more rapid than that with HBV.

NS3 Protease Inhibitors

The HCV NS3 protease, which is necessary for viral replication, has an exposed active site that has made development of small molecules that tightly...
bind the site difficult. The geometry of the active site also increases the potential for cross-resistance because there are only a limited number of “good” contacts that small molecule inhibitors can make with the binding site. Despite the challenges in design, NS3 protease inhibitors were the first class of direct-acting anti-HCV drugs validated in the clinic and are the furthest along in clinical trials.

When used in combination with standard-dose peginterferon alfa plus ribavirin therapy, NS3 protease inhibitors may increase SVR rates in patients with HCV genotype 1 from 40% to as high as 75%. Randomized phase II trials of telaprevir and boceprevir (investigational drugs in this class that are now in phase III trials) showed SVR rates substantially higher than those achieved with 48 weeks of peginterferon alfa plus ribavirin treatment. In the phase II trials, telaprevir was administered for 12 weeks and peginterferon alfa plus ribavirin for 24 weeks or 48 weeks. Boceprevir was administered with peginterferon alfa plus ribavirin for 28 weeks or 48 weeks (Figure 1). Two additional arms in the boceprevir study looked at a 4-week lead-in with peginterferon alfa and ribavirin, followed by 24 weeks or 44 weeks of triple-combination therapy. The 4-plus-44-week arm had the highest SVR rate at 75% (Hézode et al, N Engl J Med, 2009; Kwo et al, EASL, 2009; McHutchison et al, N Engl J Med, 2009).


Shorter durations of peginterferon alfa plus ribavirin treatment were associated with greater relapse (posttreatment) and, in some cases, lower SVR rates; the omission or use of lower doses of ribavirin was also associated with poorer outcome. Telaprevir was associated with severe rash in 5% to 7% of patients (vs 0%–1% in patients receiving peginterferon alfa plus ribavirin) and an additional decline in hemoglobin level of approximately 0.5 g/dL. Viral breakthrough occurred in 7% to 10% of patients receiving telaprevir; 90% to 95% of patients who experienced breakthrough and 95% of patients who had relapsed had virus with resistance mutations. Boceprevir was associated with anemia in 52% to 63% of patients compared with 34% of patients in the peginterferon alfa plus ribavirin control group and was associated with dysgeusia in 21% to 44% versus 9%, respectively. With both investigational drugs, discontinuation rates were higher in the HCV NS3 protease inhibitor groups than in the control groups.

**NS5B Polymerase Inhibitors**

There are several sites on NS5B polymerase that can serve as drug targets, including the active site targeted by nucleoside analogue NS5B inhibitors and 2 sites each on the “palm” and “thumb” of the polymerase structure that are targeted by nonnucleoside analogue NS5B inhibitors. Two main categories of nucleoside analogue NS5B polymerase inhibitors exist: (1) compounds that feature a 2′-C-methyl group and (2) compounds with a 4′-azido group. As an example of activity observed with these drugs, the 2′-C-methyl compound R7128 (a prodrug of the nucleoside analogue PSI-6130) was associated with a 2.7 log_{10} IU/mL reduction in HCV RNA level at 1500 mg twice daily and a 5 log_{10} IU/mL reduction when administered in combination with peginterferon alfa plus ribavirin. R7128 was also associated with a rapid virologic response rate of 75% in a phase I evaluation. The drug is now undergoing phase II testing at doses of 1000 mg and 1500 mg twice daily (Lalezari et al, EASL, 2008).

A 4′-azido compound, R1626 (a prodrug of the nucleoside analogue R1479), produced a 5.2 log_{10} IU/mL reduction in HCV RNA level when administered with peginterferon alfa plus ribavirin but was associated with hematologic toxicity that required dose modification in 90% of patients and discontinuation of treatment in 50%; it also resulted in a high relapse rate. Thus, clinical development was halted after the phase II trial (Pockros et al, Hepatology, 2008).

The prodrug of a uridine nucleotide analogue, PSI-7851 was developed based on findings that the minor intracellular uridine metabolite of PSI-6130 had a longer half-life and reached substantially higher triphosphate levels in cells than the parent drug. Early-phase testing of PSI-7851 showed that a 400-mg, once-daily dose was associated with a reduction in HCV RNA of approximately 2 log_{10} IU/mL. PSI-7851,
as well as PSI-7977 (a racemically pure form), continue in phase II evaluation (Rodriguez-Torres et al, AASLD, 2009; Furman et al, AASLD, 2008).

With regard to nonnucleoside analogue NS5B polymerase inhibitors, the 2 palm sites have considerable overlap, increasing the likelihood of cross-resistance among drugs targeting these sites. The rapidity with which resistance can emerge during monotherapy is demonstrated by data on the nonnucleoside analogue HCV-796, a “palm 2” inhibitor. The highest doses of this drug administered alone were associated with reductions in HCV RNA of approximately 1.5 log10 IU/mL at day 3, with viral load rising thereafter and approaching baseline by day 14 in association with resistance mutations. Development of this drug was halted in phase II testing because of hepatotoxicity. Other investigational drugs that have advanced to phase II studies include ANA598 (a “palm 1” molecule), which yielded a 2.9 log10 IU/mL reduction in viral load at 800 mg twice daily for 4 days in a phase I study and showed cross-resistance to palm 2 compounds, and VCH-222 (a “thumb 2” compound), which produced a 3.7 log10 IU/mL reduction at 750 mg twice daily.

Other Targets

Other potential drugs with HCV targets include entry inhibitors and inhibitors of other nonstructural proteins, including nonstructural protein 4A (NS4A; serine protease cofactor), nonstructural protein 4B (NS4B; membrane alterations), and nonstructural protein 5A (NS5A; phosphoprotein). Anti-HCV drugs in development with nonviral targets include cyclophilin inhibitors and thiazolides (including nitazoxanide, an antiparasitic drug with anti-HCV activity). Antagonists of NS5A, a phosphoprotein essential for viral replication, have shown considerable activity in early evaluation. A phase 1 study of the investigational NS5A inhibitor BMS-790052 showed a reduction in viral load of approximately 3.5 log10 IU/mL that persisted for 1 week after a single 100-mg dose. This drug is likely suitable for once-daily dosing given that a 1-mg dose (which was associated with a reduction in viral load of approximately 2 log10 IU/mL in the phase I study) exhibited a plasma concentration above the 90% effective concentration (EC90) at 24 hours after dosing (Nettles et al, AASLD, 2008).

Resistance

Protease Inhibitor Resistance

Resistance to NS3 protease inhibitors emerges very rapidly in vivo, occurring within 3 days. Less than 1% of viral quasispecies carry drug resistance mutations before drug exposure; however, these variants are rapidly selected in response to drug pressure (Bartels et al, J Infect Dis, 2008). Among the first wave of NS3 protease inhibitors, hallmark resistance mutations that confer cross-resistance are A156V/T and R155K/T substitutions; both loci are within or close to the protease active site. Virus with the R155K/T mutation displays a moderate increase (10-fold−20-fold change) in the median effective concentration (EC50) while retaining replication fitness, whereas virus with the A156V/T mutation displays a large increase (>100-fold change) but has reduced fitness (Sarrazin et al, Gastroenterology, 2007).

The HCV subtype impacts drug resistance development. For example, with regard to the R155K resistance mutation, genotype 1a virus requires only 1 nucleotide change, whereas most genotype 1b isolates require a 2-nucleotide change, translating into a higher resistance barrier. To date, essentially all resistance related to the R155K mutation has been observed in patients with the HCV genotype 1a subtype (Hézode et al, N Engl J Med, 2009; McHutchison et al, N Engl J Med, 2009).

A profile of telaprevir resistance in a 14-day monotherapy study is shown in Figure 2. Use of a clonal assay that detects variants to a level of 5% of the viral population showed that all patients had wild-type virus at baseline. Some patients had undetectable virus during the 14-day dosing period, but all other patients (exhibiting either breakthrough or plateau viremia) had resistant mutants detected, with wild-type virus constituting a minority of the population (Sarrazin et al, Gastroenterology, 2007). During follow-up of 3 months to 7 months, resistant mutants emerged in patients who had undetectable virus during the 14-day study, and resistant mutants persisted in other patients. The R155K/T and V36M/A mutations were the most persistent, supporting the relative fitness of these mutant variants.

Studies with boceprevir have shown that resistant mutants can still be detected 3 years after drug exposure. The hope had been that because HCV is a “pure” RNA virus with no latent or integrated form, resistance would disappear relatively rapidly. However, these data raise the possibility of rapid reemergence of resistance upon reexposure to drug because of the persistence of relatively fit resistant variants, as occurs with HIV.

Nucleoside Analogue NS5B Polymerase Inhibitor Resistance

Resistance to nucleoside analogue NS5B polymerase inhibitors appears to be more difficult to achieve than with the NS3 protease inhibitors. Identified resistance mutations confer only a modest increase in EC50 (eg, 2-fold−5-fold change). Consistent with the concept that the mutations occur in the polymerase’s highly conserved active site, the resistant variants have markedly reduced replication fitness. For example, the S96T resistance mutation causes an approximately 3- to 5-fold increase in EC50 versus wild-type virus and has replication fitness of only 5% to 10% of that of wild-type virus. Resistance has not been detected in 14-day monotherapy studies of nucleoside analogue NS5B polymerase inhibitors and generally takes several months to select in vitro. Another consequence of the conservation of the active site is that nucleoside analogue NS5B polymerase inhibitors have exhibited consistent activity across HCV genotypes.

Two distinct resistance patterns have been found with these drugs,

**Nonnucleoside Analogue NS5B Polymerase Inhibitor Resistance**

Resistance to nonnucleoside analogue NS5B polymerase inhibitors emerges rapidly, and resistant mutants often are present before drug exposure. In a study of 92 patients with HCV genotype 1, no patients had nucleoside analogue NS5B resistance at baseline, whereas 21% of patients had preexisting nonnucleoside analogue NS5B inhibitor resistance mutations (simply reflecting the result of error-prone replication) (Le Pogam et al, *J Antimicrob Chemother*, 2008). Although the percentages of the baseline quasispecies with resistance mutations were only on the order of 1% to 3%, this level is similar to or higher than the baseline percentage that portends virologic failure with nonnucleoside analogue reverse transcriptase HIV inhibitors such as efavirenz.

**Interferon Alfa–Free Therapy?**

The INFORM-1 (Interferon-Free Regimen for the Management of HCV) trial examined results with 14-day regimens combining the nucleoside analogue NS5B polymerase inhibitor R7128 and the NS3/4A protease inhibitor R7227 (also known as ITMN-191 or danoprevir) in small groups of treatment-naïve and -experienced patients. At the highest dose tested in naïve patients, 63% (5/8) had undetectable virus (<15 IU/mL) at day 14, a 5.1 log10 IU/mL median decrease in viral load was observed, and no breakthrough resistance was detected (Gane et al, *Lancet*, 2010). Such findings raise the possibility of interferon alfa–free treatment for HCV infection. However, given what is known thus far about resistance to direct-acting antiviral drugs, such treatment will almost certainly require combinations of more than 2 drugs to raise an effective barrier to emergence of resistance.

One current model posits that all single- and 10% to 100% of double-mutant variants, depending on baseline replication levels, are likely to preexist in every HCV-infected patient (with triple mutants expected to be extremely rare). Compensatory mutations will occur within days of drug exposure through drug selective pressure. Thus, for a regimen consisting of only direct-acting agents, a barrier of 4 or more mutations is likely to be needed to prevent loss of virologic control through resistance (Rong et al, *Sci Transl Med*, 2010). It also remains unclear whether treatment can be as successful without the posited benefits of interferon alfa in improving HCV-specific CD4+CD8+ immune cell responses and reversing HCV-associated immunosuppression.

**Conclusion**

Among the direct-acting antiviral drugs furthest along in development, the NS3 protease inhibitors show potent inhibition (with reductions in viral load of 3 log10 – 4 log10 IU/mL) but a low resistance barrier. Their target geometry is also associated with an increased likelihood of cross-resistance. These drugs are likely to be the first direct-acting drugs approved by the US Food and Drug Administration, with telaprevir and boceprevir both currently in phase III trials.

Among the NS5B polymerase inhibitors, the nucleoside analogues show cross-genotype and cross-subtype activity and exhibit a high resistance barrier (with 2 distinct resistance profiles), but concerns with tolerability and adverse effects remain. The nonnucleo-
side analogue NS5B inhibitors have several target sites, but intrinsic (i.e., preexisting) resistance and a low barrier to resistance (including cross-resistance at palm sites) remain problems for this class in general. These drugs have also exhibited variable activity across HCV genotypes and subtypes. The initial use of direct-acting drugs will be as add-on treatment to peginterferon alfa plus ribavirin therapy. The successful development of interferon alfa–sparking regimens depends on achieving a sufficiently high barrier to resistance and whether the immunomodulatory effects of interferon alfa are needed for cure of HCV infection.

Studies are ongoing in patients coinfected with HIV and HCV, including phase II studies of telaprevir and boceprevir and a pilot trial of nitazoxanide plus peginterferon alfa and ribavirin. To date, all studies are enrolling interferon alfa–naive patients with HCV genotype 1 infection. An issue that researchers, academics, and practitioners in infectious diseases should follow is that pharmaceutical companies will develop their own combinations of direct-acting drugs. These combinations may not necessarily reflect the most promising options available from all compounds in development, in terms of activity, tolerability, and resistance emergence. As was done during development of HIV therapeutics, pressure should be brought to advocate for the early study of promising drug combinations, even across company lines, to ensure that patients have access to the best possible treatment regimens as soon as possible.

Presented by Dr Wyles in May 2010. First draft prepared from transcripts by Matthew Sienger. Reviewed and edited by Dr Wyles in September 2010.

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Suggested Reading


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Care of HIV-Infected Women During Pregnancy
Deborah Cohan, MD, MPH
CME Credit Available: 2.0 AMA PRA Category 1 Credits™
Level: Advanced

Although remarkable strides in HIV medicine have dramatically lowered the risk of perinatal HIV transmission, clinicians continue to encounter numerous challenges in providing care for HIV-infected pregnant women. This COW activity addresses the risk of birth defects resulting from antiretroviral therapy and identifies treatment regimens that pose low risk to the woman and the fetus. Indications for elective cesarean delivery, as well as postpartum management of HIV disease, are discussed. This activity also presents the particularly challenging situation of HIV infection diagnosed late in pregnancy.

Viral Blips in the HIV-Infected Patient
Timothy J. Henrich, MD, and Daniel R. Kuritzkes, MD
CME Credit Available: 1.5 AMA PRA Category 1 Credits™
Level: Advanced

Episodes of intermittent low-level viremia (ie, viral blips) are often detected during routine laboratory monitoring of HIV-infected patients. Viral blips may lead clinicians to order unnecessary tests and alter medication regimens for patients whose infection is otherwise well controlled. This COW presentation discusses the sparse and sometimes conflicting research about the etiology of blips. The relationship of blips to medication adherence and antiretroviral drug resistance, as well as management strategies for patients with blips, are also described.

Common Bacterial Infections in the HIV-Infected Patient
Ricardo M. La Hoz, MD, and J. Martin Rodriguez, MD
CME Credit Available: 1.75 AMA PRA Category 1 Credits™
Level: Advanced

During the past decade, incidence of Clostridium difficile infection (CDI) and community-associated methicillin-resistant Staphylococcus aureus skin and soft-tissue infections has increased dramatically. These infections are especially common in HIV-infected individuals. This COW activity details the risk factors, clinical presentation, and treatment of each condition, and management of recurrent episodes of CDI is also discussed.

Cases on the Web (COW) is a series of case-driven continuing medical education activities sponsored by the IAS–USA. The COW program was created to offer physicians convenient online access to top-quality education in the field of HIV medicine.

NEW
Treatment of Opioid Dependence in Patients with HIV/AIDS
Hillary Kunins, MD, MPH, MS, and Chinazo Cunningham, MD, MS
CME Credit Available: 1.75 AMA PRA Category 1 Credits™
Level: Advanced

HIV-infected patients with opioid dependence can now receive buprenorphine treatment in HIV care, primary care, or substance abuse treatment settings. Offering colocated treatment provides the opportunity to improve HIV outcomes and to reduce substance use among patients. This COW presentation discusses the use of opioid agonist medications and explains specific pharmacotherapeutic properties of buprenorphine that can pose challenges in clinical practice.

NEW
Human Papillomavirus Infection in the HIV-Infected Woman
Erna Milunka Kojic, MD, and Susan Cu-Uvin, MD
CME Credit Available: 1.75 AMA PRA Category 1 Credits™
Level: Advanced

The widespread use of potent antiretroviral therapy has resulted in dramatic improvements in life expectancy among HIV-infected women, but the incidence of human papillomavirus (HPV)-related diseases remains high and continues to rise. This COW presentation discusses the epidemiology of HPV among HIV-infected women, explains the effect of antiretroviral therapy on HPV-related anogenital diseases, and reviews the use of the prophylactic HPV vaccine.

NEW
Management of Depression and Alcohol Dependence in an HIV/HCV Coinfected Patient
Gareen Hamalian, MD, MPH, and Joseph Z. Lux, MD
CME Credit Available: 1.5 AMA PRA Category 1 Credits™
Level: Advanced

Treatment of psychiatric illness in HIV-infected patients, especially when this illness is accompanied by substance abuse, is a common and complex concern for HIV health care providers. On completion of this COW activity, the learner will be able to compare psychopharmacologic treatment options for depressed HIV-infected patients, discuss neuropsychiatric concerns related to the use of efavirenz, and discuss prophylaxis and treatment options for HIV/hepatitis C virus coinfected patients on interferon alfa therapy.

For information about any of these Cases on the Web, please contact the International AIDS Society–USA.
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**Perspective**

**Sexually Transmitted Infections and HIV: Epidemiology and Interventions**

*Although the association of HIV and sexually transmitted infections (STIs) has been well known for 25 years, there is insufficient attention to STIs by many HIV providers, in part because patients are asymptomatic or have nonspecific symptoms and because of provider demands and focus. Optimal patient care requires frequent testing for STIs as well as obtaining an accurate medical history, which requires building trust with patients and asking direct but open-ended questions about risks and symptoms. Increased vigilance will also help practitioners avoid missing these infections. Herpes simplex virus type 2 infection has highly variable clinical manifestations, and diagnosis is needed before considering episodic or suppressive treatment. However, suppressive treatment of herpes simplex virus type 2 infection has not been shown to reduce risk of HIV acquisition. The increase in syphilis rates continues; screening is inexpensive and treatment is highly effective. Quinolone resistance rates in gonorrhea are increasing, complicating treatment in some locales. Cases of proctitis caused by chlamydial infection with lymphogranuloma venereum strains have been observed in the United States and Europe. This article is a summary of a presentation by Connie L. Celum, MD, MPH, at the International AIDS Society–USA continuing medical education program held in March 2010 in New York City.*

Sexually transmitted infections (STIs) are commonly underdiagnosed by HIV care practitioners. Thus, it is important to increase vigilance and recognize that STIs are often asymptomatic or have nonspecific symptoms, that their presence can increase HIV infectiousness, and that regular testing for STIs is needed to ensure optimal treatment of HIV-infected patients.

**Herpes Simplex Virus Type 2 Infection**

Twenty years’ worth of epidemiologic data support a synergistic relationship between herpes simplex virus type 2 (HSV-2) and HIV infections. Reactivation of HSV-2 increases HIV susceptibility and infectiousness and potentially accelerates HIV disease progression. Also, HIV infection increases the frequency of HSV-2 outbreaks, facilitating HSV-2 transmission. Numerous longitudinal studies that were adjusted for age and sexual behavior have shown that prevalent HSV-2 infection is associated with a statistically significant increase in the relative risk (RR) of HIV acquisition in men (RR, 2.7), women (RR, 3.1), and men who have sex with men (MSM; RR, 1.7). The risk of HIV acquisition appears to be even higher in patients with incident (recently acquired) HSV-2 infection (RR, ~6), although it is difficult to discern whether individuals acquired HSV-2 infection before or at the same time as HIV infection. In some African locales where HSV-2 prevalence is very high, mathematical modeling and epidemiologic analyses estimate that up to one-third to one-half of new HIV infections can be attributed to HSV-2 infection.

Biological plausibility for increased HIV susceptibility comes from various lines of evidence. These include studies showing that HSV-2 causes macroscopic and microscopic ulcerations and that HSV-2 reactivation is quite frequent. Studies of HIV-seronegative persons in which patient-obtained genital swabs were tested by HSV polymerase chain reaction show that reactivation occurs on 20% of days and even more frequently if HSV shedding is evaluated more than once daily (Mark et al, *J Infect Dis*, 2008). Also, HSV-2-infected women who were not necessarily shedding virus had increased populations of HIV target cells, specifically immature dendritic cells and cervical CD4+ T cells expressing CC chemokine receptor 5 (CCR5) (Rebbapragada et al, *AIDS*, 2007).

Such data provided the rationale for investigating whether suppression of HSV-2 could reduce acquisition of HIV. In a placebo-controlled study in 821 HSV-2-seropositive, HIV-seronegative Tanzanian women at high risk of HIV infection—a study in which the drop-out rate was high, adherence was modest, and clinic visits occurred only quarterly—twice-daily acyclovir 400 mg showed no effect in preventing HIV acquisition (Watson-Jones et al, *N Engl J Med*, 2008). Another trial conducted with the same acyclovir dose in more than 3000 HSV-2-seropositive, HIV-seronegative women in African locales and MSM in Peru and the United States also showed no preventative effect in HIV acquisition (Celum et al, *Lancet*, 2008).

A potential explanation for why HSV-2 suppression did not reduce risk of HIV acquisition is provided by recent data supporting a “sparks-and-embers” model of continued susceptibility even in patients with suppressed HSV-2 outbreaks. These data show that as the host genital mucosal immune system persistently encounters HSV-2 antigen, localized persistence of CCR5+ cells is imprinted in genital skin and mucosa, resulting in a 10-fold increase in CD4+ cells and dendritic cells in the genital epithelium that lasts for more than 8 weeks after HSV-2 reactivation (Zhu et al, *Nat Med*, 2009). The increased infiltration of HIV target...
cells (“sparks”) and increased local enhancement (“embers”) provides HIV with an advantage in an initial contact between HIV and host. Although current HSV-2 drugs can suppress reactivation, they do not reduce the persistent inflammation of the genital mucosal HIV target cells. Thus, the susceptibility to HIV acquisition remains increased.

Other studies have evaluated whether suppression of HSV-2 in patients coinfected with HIV can reduce HIV infectiousness or HIV disease progression. The plausibility of such effects is supported by a number of findings. First, data from the pre-potent antiretroviral therapy era indicated that the addition of high-dose acyclovir to nucleoside analogue reverse transcriptase inhibitor (nRTI) treatment improved survival. Second, HSV-2 reactivation is more frequent in HIV-infected persons than in uninfected persons. Lesions persist longer and high amounts of HIV RNA are present in lesion fluid (exceeding plasma levels). Third, increased levels of plasma and genital HIV RNA are present during even asymptomatic HSV-2 reactivation. Fourth, HSV proteins produced during reactivation have been demonstrated to upregulate HIV replication in vitro. Finally, numerous studies (generally small and with short follow-up periods) have shown that in HIV-infected persons with CD4+ cell counts greater than 250 µL who are not receiving antiretroviral therapy, acyclovir or valacyclovir suppressive therapy is associated with reductions in HIV RNA levels in plasma (by 0.3 log_{10}–0.5 log_{10} copies/mL) and in rectal, seminal, and cervical secretions.

In the recent Partners in Prevention HIV and HSV transmission study conducted in 7 countries in Africa, each HIV- and HSV-2-coinfected person in 3400 HIV-serodiscordant couples was randomly assigned to receive twice-daily acyclovir 400 mg or placebo, and the couples were observed for up to 2 years (Celum et al., N Engl J Med, 2010; Lingappa et al., Lancet, 2010). The HIV-infected partners had CD4+ cell counts of 250 µL or greater (the national guidelines threshold for initiating antiretroviral therapy) and were not receiving antiretroviral therapy at study entry. Over the 2 years, acyclovir treatment was not associated with a statistically significant prevention of HIV acquisition (hazard ratio, 0.92; 95% confidence interval, 0.60–1.41; P = .69), despite a 0.25 log_{10} copies/mL reduction in plasma HIV RNA level and a 0.75 log_{10} copies/mL reduction in genital ulcer secretions. However, acyclovir suppression was associated with a statistically significant 16% reduction in HIV disease progression measured as the composite of decrease in CD4+ cell count to less than 250 µL, initiation of antiretroviral treatment, or death. Treatment was also associated with a statistically significant 19% reduction in progression to CD4+ cell counts of less than 350/µL in patients entering the study with counts above this level.

The lessons learned from the recent intervention studies include the following: a suppressive regimen (twice-daily acyclovir 400 mg) does not resolve persistent inflammation caused by HSV infection; such suppressive treatment does not prevent HIV transmission despite reductions in HSV-2 outbreaks and a 0.25 log_{10} copies/mL reduction in plasma HIV RNA levels; and twice-daily acyclovir 400 mg modestly reduces progression of HIV disease in patients not receiving antiretroviral therapy who have CD4+ cell counts of 250 µL or greater.

One conclusion is that for patients coinfected with HIV and HSV-2, practitioners could consider initiating antiretroviral therapy earlier for those with CD4+ cell counts greater than 350 µL to reduce their likelihood of HIV transmission and for clinical benefits. Another conclusion is that further consideration should be made of the potential use of HSV-2 suppressive treatment in coinfected patients with CD4+ cell counts greater than 350/µL who are not eligible for or who elect not to initiate antiretroviral therapy. A third conclusion is that more effective drugs for HSV-2 infection are needed, as is a genital herpes vaccine. Unfortunately, the recently released results of the Herpevac Trial for Women (co-sponsored by the National Institute of Allergy and Infectious Diseases and GlaxoSmithKline) of a candidate HSV-2 vaccine in HSV-1- and HSV-2-seronegative women showed no efficacy, and the pipeline for other HSV-2 vaccine candidates is limited.

The interaction of HSV-2 and HIV infections emphasizes the importance of genital herpes testing and appropriate counseling. Type-specific HSV-2 serology tests may be useful for patients with recurrent and atypical symptoms and negative culture results, for patients with a clinical diagnosis of HSV-2 but no laboratory confirmation, and for patients with a sexual partner with genital HSV infection. Type-specific testing might also be appropriate for patients presenting for comprehensive STI evaluation, for those with HIV infection or several sexual partners, and for MSM with high risk of acquiring HIV. Type-specific enzyme immunoassays (EIAs) for HSV-2 have sensitivity and specificity of 97%, and results can be expected to become positive within 3 weeks after the acquisition of HSV-2 infection. Updated STI guidelines are expected soon from the US Centers for Disease Control and Prevention (CDC) regarding recommendations for serologic testing for HIV-infected patients and for those with high-risk behaviors for HIV acquisition.

**Syphilis**

The recent increase in incidence of syphilis shows no sign of slowing. Increased syphilis rates have been observed in the last 7 consecutive years for which there are data (Figure 1). Currently, rates are 6 times higher in men than women and 7 times higher in blacks than whites; approximately two-thirds of cases are in MSM, many of whom are coinfected with HIV. Regarding risk factors for HIV-1 acquisition, the data for early syphilis and other non-HSV causes of genital ulcer disease are less clear and consistent than are the data for HSV-2 causes. However, there is an ongoing epidemic of primary and secondary syphilis among MSM in US cities and some European cities, with a majority of cases identified among HIV-infected MSM. Given that serologic screening is sim-
Patients with secondary syphilis exhibit hepatosplenomegaly, alopecia, and other nongenital manifestations.

The differential diagnosis of syphilis includes rash associated with antiretroviral therapy, tinea versicolor, pityriasis rosea, generalized scabies, fixed drug eruption, erthyema multiforme, and psoriasis. It is important to maintain a high degree of suspicion for syphilis and to order serologic testing for asymptomatic patients. Titers should be monitored for 6 months to 12 months for patients with primary or secondary syphilis, as titers may persist at higher levels than previously thought.

Most syphilis is diagnosed through serologic screening. The new screening paradigm is to first use treponemal tests (ie, EIAs or chemiluminescence immunoassays specific to Treponema pallidum). Such assays provide qualitative results and reactivity that persists over a lifetime. Nontreponemal (eg, rapid plasma reagin [RPR] and VDRL) tests are then used to obtain quantitative results necessary for clinical management. The treponemal tests are highly automated, less costly, and easier to perform than the nontreponemal tests. However, false-positive results can occur with treponemal tests, presenting diagnostic challenges in low-prevalence populations.

Latent syphilis is divided into early latent (<1 year) or late latent (>1 year) syphilis for treatment purposes. Syphilis of unknown duration is managed the same way as late latent syphilis. Latent syphilis is diagnosed according to symptoms and history of test results. If a patient undergoes annual testing and a positive test result occurs at some point, a diagnosis of early latent disease can be made comfortably. Criteria for early latent syphilis include negative serology results in the past year, known exposure to someone with an early case of syphilis, clear history of typical signs and symptoms in the past year, positive serology results in a patient whose only exposure came within the past year, and a 4-fold increase in titer in the past year. The last criterion might also indicate treatment failure and may provide rationale for performing lumbar puncture (LP).

The decision to perform LP for examination of cerebrospinal fluid (CSF) in latent syphilis is fairly straightforward for patients with neurologic or ophthalmic signs or symptoms, evidence of tertiary disease (gumma, aortitis), or treatment failure (eg, 4-fold rise in titers). In patients with HIV infection, CSF examination should also be performed in those with late latent syphilis or latent disease of unknown duration in the presence of neurologic symptoms. LP should also be considered in HIV-infected patients with syphilis at any stage and CD4+ cell counts of 350/µL or less and RPR titer greater than or equal to 1:32. Diagnostic specificity for asymptomatic neurosyphilis is improved by using a CSF pleocytosis cutoff value of greater than 20 white blood cells/mL. Recent data indicate that in immunocompetent patients—eg, HIV-infected patients receiving antiretroviral therapy—normalization of serum RPR titer is predictive of normalization of CSF parameters, which may reduce the frequency needed for follow-up LPs.

Treatment of primary, secondary, or early latent syphilis in adults is with long-acting penicillin G benzathine (2.4 million units, single-dose...
intramuscular injection). No data support benefits of higher doses, additional doses, or longer treatment with penicillin G benzathine, amoxicillin, or other antibiotics. Other treatment options (eg, for nonpregnant, penicillin-allergic adults) include oral doxycycline (100 mg twice daily for 2 weeks), oral tetracycline (500 mg 4 times daily for 2 weeks), and intravenous or intramuscular injections of ceftriaxone (1 g daily for 10–14 days). When possible, it is preferable to avoid the doxycycline and tetracycline regimens, given the importance of patient adherence. Oral azithromycin (2 g, single dose) is also an option, although most practitioners currently recommend avoiding it (and not using it for MSM or pregnant women) because of recent data suggesting problems with drug resistance.

Gonorrhea

The major new concern in gonorrhea management is the emergence of quinolone resistance. The new nucleic acid amplification tests (NAATs) work well for diagnosis but do not identify antibiotic resistance. The potential presence of quinolone-resistant infection in patients who have traveled to locales with high rates of quinolone resistance or who are not responding to quinolone therapy should prompt the order of a culture. Routine annual screening of exposed sites—eg, urethra, pharynx, and rectum—should be performed. Retesting should be performed after treatment.

Recommended treatment is cefixime (oral, 400 mg) or ceftriaxone (intramuscular injection, 250 mg). Other treatment options include oral cepodoxime (400 mg), oral cefuroxime (1 g), and single-dose injectable cefalosporin regimens. Single-dose oral quinolone regimens are also an option, although many practitioners avoid using quinolones because of the increasing problem with resistance. Patients should be treated empirically and concurrently for chlamydial infection, unless it is ruled out by results from a highly sensitive test (ie, NAAT).

Treatment options for cephalosporin-allergic patients have become more limited since the removal of spectinomycin from the US market. The CDC currently recommends allergy desensitization procedures but recognizes this is not possible for many patients. A regimen of 2 g of azithromycin can be considered, but patients need to be prepared for the gastrointestinal side effects associated with this dose. Further, resistance to azithromycin is increasing, and treatment failures have been observed. If possible, cultures to determine drug sensitivity should be performed before treatment; if not, test-of-cure procedures should be performed at 3 days to 5 days by culture or at 3 weeks by NAAT. Some locales still have low rates of quinolone resistance associated with gonorrhea, thus practitioners need to stay abreast of the local epidemiology and upcoming CDC STI treatment guidelines.

Proctitis

The differential diagnosis of proctitis includes HSV infection (typically, primary episode), gonorrhea, and Chlamydia trachomatis infection, including infection with strains that cause lymphogranuloma venereum (LGV). LGV is frequently associated with inguinal lymphadenopathy (buboes) and genital ulcer. Characteristics of recent cases of LGV proctitis in the United States include a tendency for delayed diagnosis and presentations typically occurring in HIV-infected MSM with a history of unprotected receptive anal sex. Practitioners should consider ordering cultures for C trachomatis rather than using NAAT for diagnosing proctitis in such patients.

The treatment recommendations for uncomplicated chlamydial infection are azithromycin (1 g single dose) and doxycycline (100 mg twice daily for 7 days). Alternative treatment options include erythromycin (base, 500 mg 4 times daily for 7 days), erythromycin succinate (800 mg 4 times daily for 7 days), ofloxacin (500 mg twice daily for 7 days), or levofloxacin (500 mg daily for 7 days). These regimens are 97% to 98% effective, generally eliminating the need for test-of-cure procedures. For patients with LGV, doxycycline must be administered for 3 weeks instead of 7 days.

Human Papillomavirus Infection

Human papillomavirus (HPV) DNA testing is clinically useful for triage of Papanicolaou smears indicating atypical squamous cells of undetermined significance in women more than 20 years old and for adjunctive screening in women 30 or more years old. It has no proven benefit in deciding whether to provide HPV vaccination, STI screening, triage of low-grade squamous intraepithelial lesions or of higher-grade lesions in adults, testing of adolescents younger than 21 years old, evaluation of sexual partners, or evaluation of genital warts.

The HPV vaccine is recommended in girls and women aged 9 years to 26 years for prevention of cervical cancer, genital warts, and precancerous lesions of the cervix, vagina, and vulva. Available data indicate that the vaccine has no preventive effect in women already infected with HPV. The vaccine has been shown in ongoing trials to be safe and immunogenic in HIV-infected women; however, most HIV-infected women already have HPV infection. Data for HIV-seronegative men indicate efficacy of the vaccine in preventing genital warts and precancerous lesions; an advisory panel of the US Food and Drug Administration recommended approval of the vaccine in such patients.

Screening and Prevention

The primary principles of evaluating patients for STIs are that practitioners need to actively examine patients for signs and symptoms and elicit full histories from their patients. For preventive efforts to be successful, patient sexual history must be obtained routinely, and patients must be counseled regularly about risk reduction. Screening is crucial because so many conditions are asymptomatic. Patients should be informed about which STIs they are tested for and which not; too often, patients assume they have had a negative result for a test that was
never performed. Patient history about behaviors and anatomic sites of exposure should guide the selection and frequency of screening tests. For MSM, screening should include serologic testing for HIV after oral or anal exposure, syphilis after any unprotected exposure, HSV-2 at initial evaluation, gonorrhea and chlamydial infection in the urethra or in urine after oral or anal exposure and in the rectum after receptive anal intercourse, and gonorrhea in the pharynx after receptive oral intercourse. Testing should be done at least annually and more frequently in patients with increased risk.

Presented by Dr Celum in March 2010. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Celum in October 2010.

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Suggested Reading


**Perspective**

**Current Issues in the Diagnosis and Management of Tuberculosis and HIV Coinfection in the United States**

Approximately 10% of new cases of tuberculosis (TB) in the United States occur in HIV-infected persons. HIV infection dramatically increases the risk of TB, and this increased risk is present throughout the course of HIV infection. TB and HIV coinfection complicates the course and treatment of both diseases. Isoniazid preventive therapy and antiretroviral therapy both substantially reduce the risk of developing active disease in persons with latent TB infection. Antiretroviral therapy should be given during treatment for active TB, as mortality was reduced by 56% with initiation of antiretroviral therapy before the completion of TB therapy. In addition, for patients with low CD4+ cell counts (< 200/µL), starting antiretroviral therapy during the intensive phase of TB treatment reduced mortality by 34% compared with delaying antiretroviral therapy until 8 weeks after TB treatment initiation. This article summarizes a presentation by Anne F. Luetkemeyer, MD, at the International AIDS Society–USA continuing medical education program held in May 2010 in San Francisco.

In 2008, 1.37 million new cases of tuberculosis (TB) occurred in HIV-infected persons worldwide, with an estimated nearly half-million deaths due to TB in HIV-infected individuals (World Health Organization, 2009). Prevalence rates of TB in HIV infection are highest (≥ 50%) in areas of sub-Saharan Africa and are substantial in many other locales worldwide (Figure 1). Globally, TB is one of the most frequent causes of mortality in HIV disease, accounting for an estimated one-third of AIDS-related deaths in some series. Extraordinarily high mortality rates are associated with multidrug resistant (MDR) and extensively drug resistant (XDR) TB in HIV coinfection.

In the United States, an 11.4% decrease was reported in TB incidence in 2009 from 2008, although this figure may represent underreporting (Centers for Disease Control and Prevention, MMWR, 2010). Approximately 50% of new TB cases occurred in California, New York, Florida, and Texas. HIV coinfection is present in approximately 10% of new TB cases, and the rate of coinfection has plateaued over the past several years after gradually decreasing through the 1990s (Figure 2). One of the drivers of TB infection is reactivation disease in foreign-born individuals, which accounts for up to 77% of active infections (Cattamanchi et al, *Int J Tuberc Lung Dis*, 2006). Nationwide, 60% of TB cases occurred in foreign-born individuals, exceeding the TB rate in individuals born in the United States. Since 2003, the TB rate in US-born individuals has declined more rapidly than the rate in the foreign-born population (Figure 3). Effective diagnosis and treatment of latent TB infection (LTBI) in at-risk individuals is key for TB reduction in the United States. Ongoing challenges to implementation of current US guidelines for diagnosis and treatment of LTBI have limited effective LTBI therapy (Walter et al, *Clin Infect Dis*, 2008). These data suggest that TB in the United States is here to stay and will continue to be a concern for high-risk populations such as those infected with HIV.

**Bidirectional Effects of Tuberculosis and HIV Coinfection**

Coinfection with HIV may worsen the course and complicate the diagnosis and management of TB. The effects of HIV infection on TB include altered clinical presentation, such as increased paucibacillary and disseminated TB, which increases the challenge of making an accurate and timely diagnosis.

Throughout the course of HIV disease, there is an increased risk of acquisition of, reactivation of, and reinfection with TB, despite treatment with antiretroviral drugs (Havlir et al, *JAMA*, 2008). Overall, HIV-infected patients have an estimated 20- to 37-fold higher risk of acquiring TB than do HIV-uninfected persons, and this risk remains elevated throughout the course of HIV disease. There is an estimated 2-fold greater risk of TB acquisition at the time of HIV seroconversion and a continuous increase in risk during CD4+ cell count decline. Patients with CD4+ cell counts less than 100/µL have a nearly 10 times higher risk of acquiring TB than do patients with counts greater than 500/µL, despite effective antiretroviral therapy (Lawn, Myer et al, *AIDS*, 2009). TB risk increases during the months immediately following antiretroviral therapy initiation, likely as the result of unmasking of unrecognized subclinical disease. Thereafter, the risk of acquiring TB decreases during effective antiretroviral therapy but never returns to the level of risk in HIV-uninfected persons (Lawn, Myer et al, *AIDS*, 2009; Lawn et al, *AIDS*, 2006).

The effects of TB on HIV infection include an increase in HIV viral load (reported in some but not all studies), further suppression of CD4+ cell count, increased risk of opportunistic infections, and increased mortality. High early mortality in TB and HIV coinfection, particularly at low CD4+ cell counts, has been observed despite antiretroviral therapy in resource-limited settings (Lawn, Little, et al, *AIDS*, 2009). Further, overlapping toxicities of drugs used to treat TB and HIV infections complicate delivery of effective therapy.

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Preventive Therapy in Latent Tuberculosis Infection

LTBI is the disease state that practitioners in the United States are most often challenged to diagnose and treat. Considerable rationale for screening for LTBI in HIV-infected persons comes from estimates that the risk of active TB is 3% to 10% per year for HIV-infected patients with a positive tuberculin skin test (TST) result (Whalen et al, AIDS, 1997; Selwyn et al, JAMA, 1992; Selwyn et al, N Engl J Med, 1989). This risk compares with a 5% to 10% lifetime risk in TST-positive persons without HIV infection (Horsburgh, N Engl J Med, 2004). Overall, the estimated lifetime risk of active TB in HIV-infected persons is approximately 20% (Horsburgh, N Engl J Med, 2004).

Isoniazid preventive therapy (IPT) and antiretroviral therapy are effective in preventing active TB in patients with LTBI. For example, a retrospective study in an observational cohort in Brazil (total of >17,000 person-years) demonstrated that risk of TB in HIV-infected patients was reduced by 52% with antiretroviral therapy alone, 68% with IPT alone, and 80% with both (Golub et al, AIDS, 2007). In the Haitian CIPRA (Comprehensive International Program of Research on AIDS) HT001 trial, antiretroviral therapy initiation was associated with a 50% reduction in TB incidence (Severe et al, N Engl J Med, 2010). A systematic review reported a 32% risk reduction for TB with isoniazid in HIV coinfection (Akololo et al, Cochrane Database Syst Rev, 2010). Isoniazid has been associated with reduced mortality when added to antiretroviral therapy in some epidemiologic settings; data from a South African cohort showed a further 53% reduction in mortality when isoniazid was added to antiretroviral therapy compared with antiretroviral therapy alone (Innes, CROI, 2010). Also, IPT has not been convincingly associated with the emergence of isoniazid resistance (Balcells et al, Emerg Infect Dis, 2006). Isoniazid treatment is generally safe and well tolerated, although monitoring is recommended particularly for patients with hepatic dysfunction.

Diagnosis of Latent Tuberculosis Infection

Tuberculin skin testing with purified protein derivative (PPD), the historical standard for diagnosing LTBI, has many limitations. These include a dependence on the operator for correct administration and interpretation of the test, an association with false-positive results stemming from cross-reactivity with nontuberculous mycobacteria, and the requirement for a return patient visit within a specified time window for results to be read. In many US urban clinics, the return visit rate for TST interpretation may be as low as 35% (Chaisson et al, J Acquir Immune Defic Syndr Hum Retrovirol, 1996).

Interferon gamma (IFN-γ) release assays (IGRAs) are alternative tests for LTBI diagnosis. IGRAs measure levels of IFN-γ released after incubation with mycobacterial antigens that are more specific to Mycobacterium tuberculosis than those used in the TST. Two IGRAs are approved by the US Food and Drug Administration for commercial use in the United States; one assay measures free IFN-γ and the other, an enzyme-linked immunosorbent spot (ELISPOT)—based assay, measures IFN-γ-releasing cells. Unlike for the TST, IGRAs do not currently have different cutoff values based on TB risk categories, including HIV infection. Therefore, results are given simply as positive, negative, or indeterminate. Some false-positive results have been observed in M kansasii.

Clinicians need to recognize that an indeterminate result on an IGRA means that the result cannot be interpreted because of either an inability of the antigen to stimulate cells or an excessive background IFN-γ level. An indeterminate result does not suggest that the test is likely negative or positive. The test can be repeated, which may yield an interpretable result. However, if a second result is indeterminate, further IGRA testing is not advisable until there has been a change in the patient’s immune status (eg, after initiating antiretroviral therapy). A second indeterminate result should be followed with a TST or, if there is concern regarding active pulmonary TB, a chest x-ray. In patients with HIV infection, both types of IGRA are more likely to yield indeterminate results at lower CD4+ cell counts, with estimated frequencies of indeterminate results of 15% to 16.5% at counts less than 100/µL and 8% to 11% at counts of 100/µL to 200/µL (Hoffmann and Ravn, *Eur Infect Dis*, 2010). However, positive or negative results from IGRA testing in patients with lower CD4+ cell counts are considered reliable for use in clinical decision making.

### Active Tuberculosis Infection

The clinical presentation of TB in HIV infection is affected by the degree of underlying immune suppression. At CD4+ cell counts greater than 350/µL, TB disease is most often limited to the lungs, histopathologic results are similar to those in HIV-seronegative patients (ie, granuloma with or without caseation), and extrapulmonary involvement, when present, usually is nodal or pleural (Burman and Jones, *Semin Respir Infect*, 2003). In advanced HIV infection, pulmonary involvement is still the most common TB presentation; however, extrapulmonary involvement is observed in approximately 70% of patients with CD4+ cell counts less than 100/µL, and up to 50% of those with CD4+ cell counts greater than 50/µL will have positive TB blood cultures. Histopathologic examination reveals poorly formed or absent granuloma. On radiography, classic findings such as cavities are less common with CD4+ cell counts less than 350/µL, and up to 21% of patients have a chest x-ray that appears normal despite sputum that is TB culture-positive (Chamie et al, *Int J Tuberc Lung Dis*, 2010; Burman and Jones, *Semin Respir Infect*, 2003).

With regard to testing, negative TST or IGRA results cannot rule out active TB. IGRA testing, for example, has a sensitivity for active disease that ranges from 80% to as low as 60% in some studies. Negative results from sputum smears also do not rule out TB, particularly in HIV infection; 50% to 62% of HIV-infected patients with positive results from pulmonary TB culture have negative acid-fast bacillus (AFB) smear results (Monkongdee et al, *Am J Respir Crit Care Med*, 2009; Getahun et al, *Lancet*, 2007). Although associated with a lower TB burden, untreated smear-negative pulmonary TB is a well-documented source of TB transmission (Tostmann et al, *Clin Infect Dis*, 2008; Hernández-Garduño et al, *Thorax*, 2004; Behr et al, *Lancet*, 1999). Even the gold standard of culture for TB can be imperfect; culture-negative clinical TB is a well-recognized entity. Thus, clinical suspicion for TB is essential in appropriately diagnosing and excluding TB in HIV infection.

Rapid TB diagnostic tests have been developed, including nucleic acid-based tests that can detect both TB and rifampin resistance with results available in less than 1 day; these will be extremely useful for HIV patients, in whom AFB smear is particularly
unreliable. One promising rapid polymerase chain reaction (PCR)–based TB diagnostic test has been shown to have a sensitivity of 99% to 100% in AFB-positive samples and 71% to 90% in AFB-negative samples (Boehme et al, N Engl J Med, 2010; Helb et al, J Clin Microbiol, 2010). However, these tests are not yet commercially available in the United States.

Issues in the Treatment of Tuberculosis and HIV Coinfection

Recommendations for treatment of drug-susceptible TB in HIV-infected patients are essentially the same as for HIV-uninfected patients, with a standard 6-month rifamycin-based regimen that is extended to 9 months in cases of delayed clinical or microbiologic response (as indicated by positive culture or continued symptoms at 2 months). Patients with CD4+ cell counts less than 200/µL should receive daily therapy (Burman, Clin Chest Med, 2005).

Recent data have helped clarify the optimal timing for initiating antiretroviral therapy in patients being treated for TB. The SAPIT (Starting Antiretroviral Therapy at Three Points in Tuberculosis Therapy) trial in South Africa demonstrated that antiretroviral therapy should not be deferred until TB treatment is completed. Virologic response was not compromised and mortality was reduced by 56% when antiretroviral therapy was initiated before completion of TB therapy (Abdool Karim et al, N Engl J Med, 2010). The mortality benefit was observed for patients with CD4+ cell counts less than 200/µL as well as for patients with counts greater than 200/µL, although few deaths occurred in the latter group.

The recently reported CAMELIA (Cambodian Early Versus Late Introduction of Antiretrovirals) study found—in AFB-smear-positive, HIV-infected patients with CD4+ cell counts less than 200/µL—a mortality benefit in starting antiretroviral therapy 2 weeks after TB treatment initiation versus waiting 8 weeks to start. The CAMELIA study population had very low CD4+ cell counts, with a median of 25/µL, and the majority of subjects had counts less than 50/µL (Blanc et al, IAC, 2010). As expected, earlier initiation of antiretroviral therapy was associated with more than twice the rate of TB immune reconstitution syndrome (IRIS; incidence per 100 person-months, 4.05 vs 1.44; P < .001). Given these data, initiation of antiretroviral therapy shortly after the start of TB treatment appears safe and efficacious and may decrease mortality, particularly in those with advanced HIV disease, despite the association with an increased risk of IRIS. Ongoing trials such as ACTG (AIDS Clinical Trials Group) 5221 and the immediate– versus early–antiretroviral therapy initiation groups of SAPIT may help further clarify optimal timing for antiretroviral therapy initiation (eg, whether concomitantly with TB therapy or after the intensive phase of 4-drug TB therapy has been completed) for patients with less severely depressed CD4+ cell counts.

Rifamycins (eg, rifampin, rifabutin) are key to effective TB therapy, but use of these drugs is complicated by HIV coinfection. HIV-infected patients may be more prone to the emergence of rifamycin resistance than HIV-seronegative persons, particularly if dosing is inadequate or intermittent (Swaminathan et al, Clin Infect Dis, 2010). In addition, rifamycins have important drug interactions with many antiretroviral drugs. For example, in terms of interactions with nonnucleoside analogues reverse transcriptase inhibitors (NNRTIs), rifampin reduces the area under the concentration-time curve (AUC) to 78% of normal for efavirenz and 69% of normal for nevirapine. Efavirenz may be preferable for use with rifampin because of the somewhat greater effect of rifampin on nevirapine drug levels and concern over subtherapeutic exposure to nevirapine in patients already receiving rifampin.

In a South African study, efavirenz-based antiretroviral therapy (at standard 600-mg dosing) for non–TB-infected patients was associated with virologic outcomes that were similar to those observed for rifampin-treated TB patients, whereas nevirapine treatment was associated with inferior virologic suppression when coadministered with rifampin (Boull et al, JAMA, 2008). Although some investigators recommend an increase of efavirenz to 800 mg when coadministered with rifampin, several studies have demonstrated that the 600-mg dosage allows for adequate levels of efavirenz in the majority of patients and provides HIV virologic suppression equivalent to that in non–TB-infected patients. Rifabutin is an alternative to rifampin but must be administered at higher doses, which may lead to increased adverse effects.

If NNRTIs cannot be used (eg, because of drug resistance, pregnancy, or HIV-2 infection), protease inhibitors (PIs) are an option. Rifampin, however, dramatically reduces PI AUC and trough concentrations. Attempts to overcome this effect by increasing ritonavir or other PI dosage have resulted in considerable toxicity including hepatitis. Thus, use of rifampin with PIs is not currently recommended if other options are available.

In contrast, rifabutin results in modest increases in AUC and trough values (10% to 20%) of the PIs. Thus, the current recommendation for patients receiving ritonavir-boosted PIs is to reduce the rifabutin dose from 300 mg daily to 150 mg 3 times per week, keeping in mind that this dose of rifabutin is inadequate if PI therapy is discontinued. However, accumulating reports describe well-documented, acquired rifamycin resistance when rifabutin has been administered at 150 mg every other day in conjunction with ritonavir-boosted PIs (Boulander et al, Clin Infect Dis, 2009; Jenny-Avital and Joseph, Clin Infect Dis, 2009). Thus, higher doses of rifabutin may be indicated for patients receiving ritonavir-boosted PIs. Many clinics are now using rifabutin 150 mg daily for such patients while the ideal rifabutin dosing for coadministration with PIs is reexamined.

Raltegravir may be an option for antiretroviral treatment during TB therapy. As rifampin reduces the AUC and trough values of raltegravir (Wenning et al, Topics in HIV Medicine, 2010), dose increases in raltegravir (Wenning et al, Am J Med, 2010) of 4-drug TB therapy has been completed) for patients with less severely depressed CD4+ cell counts. Raltegravir dosage to 800 mg
twice daily. It is unclear if this dose adjustment is clinically necessary, and studies evaluating drug-drug interactions between raltegravir and rifampin are currently under way. Regarding nucleoside analogue reverse transcriptase inhibitors (nRTIs), these drugs do not have substantial drug-drug interactions with rifamycins.

New drugs are in development that may eventually offer the option of shortening TB therapy and increasing its effectiveness. The investigational adenosine triphosphate synthetase inhibitor TMC-207 has shown a 2-month culture conversion rate for MDR-TB of 48% compared with 9% for optimized background therapy (Diacon et al, N Engl J Med, 2009), and a number of novel TB drugs are in development (including PA-824, OPC-67683, and SQ109).

**Immune Reconstitution Inflammatory Syndrome**

TB IRIS appears to comprise 2 distinct syndromes. Paradoxical IRIS, consists of a worsening of TB despite effective TB treatment and often is observed in the context of initiation of antiretroviral therapy. The other form is called unmasking IRIS, which consists of a new presentation of TB (or other opportunistic infection) after antiretroviral therapy initiation, often with an atypical or exaggerated presentation (Meintjes et al, Lancet Infect Dis, 2008). The risk of IRIS increases the lower the CD4+ cell count and the shorter the time between the initiation of TB therapy and the initiation of antiretroviral therapy (Lawn et al, AIDS, 2007).

As there is no definitive test for IRIS, it is crucial to ensure that the development of another opportunistic infection or the emergence of drug-resistant TB is not mistaken for the syndrome. IRIS is usually not life-threatening and in most cases can be treated symptomatically. However, IRIS occurring in central nervous system (CNS) or meningeal TB can be severe and in some cases lethal; initiation of antiretroviral therapy in CNS TB therefore merits a heightened level of caution and close monitoring for development of IRIS. Nonsteroidal antiinflammatory drugs are often used in mild to moderate TB IRIS, but efficacy has not been convincingly demonstrated. Prednisone may be indicated for severe IRIS (1 mg/kg for 4–6 weeks, although longer treatment may be required). A 4-week course of prednisone reduces hospitalization and the need for outpatient procedures in cases of TB IRIS but may increase the risk of additional infections (Meintjes et al, AIDS, 2010). Interruption of antiretroviral therapy should be avoided if at all possible. The potential for IRIS as a possible complication should be discussed with TB patients at the start of antiretroviral therapy, as IRIS is a frequent complication during treatment of mycobacterial infections.

Presented by Dr Luetkemeyer in May 2010. First draft prepared from transcripts by Matthew Steger. Reviewed and edited by Dr Luetkemeyer in November 2010.

**Suggested Reading**


Blanc FX, Sok T, Laureillard D, et al. Significant enhancement in survival with early (2 weeks) vs. late (8 weeks) initiation of highly active antiretroviral treatment (HAART) in severely immunosuppressed HIV-infected adults with newly diagnosed tuberculosis. [Abstract THLB106.] 18th International AIDS Conference (IAC). July 18-23, 2010; Vienna, Austria.


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Tuesday, May 17, 2011  
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Chicago, Illinois  
Tuesday, June 14, 2011  
Marriott Chicago Downtown

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Tuesday, May 3, 2011  
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