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Topics in Antiviral Medicine™

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On completion of this activity, the learner will be able to:

- Discuss advances in antiretroviral therapy, HIV and metabolism, HIV/hepatitis C virus coinfection, and tuberculosis research presented at the 2014 International AIDS Conference.
- Describe typical presentations of syphilis, gonorrhea, and other sexually transmitted infections in the context of HIV infection, as well as screening practices and treatment methods for each.
- List recommendations for HIV prevention in clinical care settings, including those for HIV testing, antiretroviral therapy, preexposure and postexposure prophylaxis, risk reduction measures, and engagement of HIV-infected patients in the HIV care continuum.

This enduring material is designed for physicians and other health care practitioners who are experienced in the principles of complex chemotherapy (eg, antiretroviral therapy) and are actively treating or will be treating patients with HIV infection.

This activity is also relevant for other practitioners, including nurse practitioners, nurses, physician assistants, pharmacists, and others.

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Friday, March 20, 2015
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Tuesday, March 31, 2015
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Monday, May 18, 2015
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Perspective

Highlights of the 2014 International AIDS Conference: Update From Down Under

The 20th International AIDS Conference held in Melbourne, Australia, from July 20 through July 25, 2014, provided much new data on nucleoside analogue reverse transcriptase inhibitor–sparing antiretroviral therapy, potential consequences of switching suppressive antiretroviral regimen, antiretroviral treatment with integrase strand transfer inhibitors, effects of antiretroviral therapy on HIV-associated neurocognitive impairment, and hepatitis C virus (HCV) treatment in HIV/HCV-coinfected individuals. This article summarizes an IAS–USA continuing education webinar presented by Paul A. Volberding, MD, in August 2014, in which he focused on a few select highlights from the Conference.

Keywords: HIV, 20th International AIDS Conference, AIDS 2014, dual antiretroviral therapy, integrase inhibitors, cognitive impairment, hepatitis C virus, HCV, coinfection

The following represents the presenter’s selection of highlights from the 20th International AIDS Conference, held in Melbourne, Australia, from July 20 through July 25, 2014.

Dual Antiretroviral Therapy and Nucleoside Analogue Reverse Transcriptase Inhibitor–Sparing Regimens

The MODERN (Maraviroc Once-daily With Darunavir Enhanced by Ritonavir in a New Regimen) study compared the nucleoside analogue reverse transcriptase inhibitor (nRTI)-sparing regimen of ronavir-boostered (r) darunavir plus once-daily maraviroc with tenofovir, emtricitabine, and darunavir/r among treatment-naive, HIV-infected patients. Virologic response (plasma HIV RNA level reduced to <50 copies/mL) occurred in 86.8% of patients taking triple therapy compared with 77.3% of patients taking dual therapy at 48 weeks (adjusted difference, -9.5%; 95% confidence interval, -14.8% to -4.2%). One analysis in the MODERN study showed no substantial difference in the prediction of virologic response with genotype testing or use of a coreceptor tropism assay in either the dual- or triple-therapy groups. The triple-therapy regimen did not show noninferiority. As that was the aim of the study, the nRTI-sparing arm failed to achieve the study goals.

The GARDEL (Global Antiretroviral Design Encompassing Lopinavir/r and Lamivudine vs LPV/r-Based Standard Therapy) trial of HIV-infected, treatment-naive patients showed no statistically significant difference in rates of virologic response (HIV RNA level reduced to <40 copies/mL) at 48 weeks between lamivudine plus lopinavir/r or standard triple therapy, among all patients (88.3% vs 83.7%, respectively; \( P = .171 \)) or among those with baseline HIV RNA levels greater than 100,000 copies/mL (87.2% vs 77.9%, respectively; \( P = .145 \)).

Hazard of Switching Antiretroviral Therapy

A study from the Canadian Observational Cohort indicated that switching from a suppressive antiretroviral regimen for any reason was associated with increased risk of virologic failure (adjusted odds ratio [aOR], 1.55; \( P < .001 \)). Increased risk of virologic failure after switching was observed among women (aOR, 0.55; \( P < .001 \), for men vs women) and injection drug users (aOR, 2.85; \( P < .001 \)). No statistically significant associations between virologic failure and older age, baseline CD4+ cell count, province, or year of antiretroviral therapy initiation were observed.

Progress With Integrase Strand Transfer Inhibitors

The 48-week analysis of the SAILING (A Study of GS1349572 Versus Raltegravir [RAL] With Investigator Selected Background Regimen in Antiretroviral-Experienced, Integrase Inhibitor-Naive Adults) study, which compared the integrase strand transfer inhibitors (InSTIs)
dolutegravir and raltegravir combined with investigator-selected background therapy in HIV-infected, treatment-experienced, INSTI-naive patients was presented. Virologic failure occurred in 0 of 32 patients who received dolutegravir and 7 of 32 patients who received raltegravir, which suggested that dolutegravir may have greater potency. Virologic failure occurred in 0 of 19 patients who received dolutegravir with 2 nRTIs, 3 of 19 patients who received raltegravir with 2 nRTIs, 0 of 12 patients who received dolutegravir with 1 nRTI, and 4 of 13 patients who received raltegravir with 1 nRTI. In 1 patient taking dolutegravir without nRTIs and 3 patients with missing phenotype, virologic failure was not observed. In studies of treatment-naive patients, resistance to dolutegravir or background drugs was not observed through 96 weeks in the SPRING-2 (A Trial Comparing GSK1349572 50mg Once Daily to Raltegravir 400mg Twice Daily) trial, and 48 weeks in the FLAMINGO (Dolutegravir Compared to Darunavir/Ritonavir, Each in Combination With Dual Nucleoside Reverse Transcriptase Inhibitors [NRTIs] in ART-naive Subjects) trial.

Effect of increase in body mass index (BMI) during antiretroviral therapy on cardiovascular disease risk in the D:A:D (Data Collection on Adverse Events of Anti-HIV Drugs) study cohort (P = .11, for effect modification in adjusted models). IRR indicates incidence rate ratio. Adapted with permission from Achhra et al. 9

Antiretroviral Therapy and Neurocognitive Impairment

Neurocognitive impairment is common in HIV disease. The CHARTER (Central Nervous System [CNS] HIV Anti-Retroviral Therapy Effects Research) study has shown that improvement in neurocognitive function is possible for some patients taking antiretroviral therapy. Of more than 400 patients, a decline in neurocognitive function was observed in 22.7%, stable neurocognitive function in 60.8%, and improvement in neurocognitive function in 16.5%. Sustained viremia was associated with neurocognitive decline, with neuro-psychiatric test scores clearly worsening among patients with consistently detectable HIV RNA levels (P = .005) compared with patients who had sometimes detectable or never detectable HIV RNA levels. Stopping antiretroviral therapy was also associated with neurocognitive decline (relative risk [RR], 1.9). Other predictors of neurocognitive decline included lower serum albumin level (RR, 1.6 per 1 unit), lower hemato-crit level (RR, 1.1 per 1 unit), severe neurocognitive comorbidity (RR, 2.1 vs minimal comorbidity), history of methamphetamine use (RR, 2.1), and depression (RR, 1.02 per 1 unit on the Beck Depression Inventory). Predictors of neurocognitive improvement included higher baseline intelligence quotient, lower total protein level in cerebrospinal fluid, lower aspartate aminotransferase level, and no history of depression.

Another analysis indicated that efavirenz use is not associated with increased risk of neurocognitive impairment. In 2 large study populations, aORs for neurocognitive impairment among patients who did or did not receive efavirenz were 1.02 (P = .89) and 0.98 (P = .90), respectively. These findings may provide some reassurance about efavirenz use, given recent concerns that it may be associated with an elevated risk—albeit a low absolute risk—of suicidal ideation. Efavirenz is now recommended by the World Health Organization for use as a third drug in antiretroviral regimens for use in countries with developing economies; thus, many millions of people are being treated with this drug.

HIV and Metabolism

A study in the D:A:D (Data Collection on Adverse Events of Anti-HIV Drugs) study cohort showed that patients in the second quartile (20.9 kg/m 2-23.0 kg/m 2) and third quartile (23.0 kg/m 2-25.5 kg/m 2) of pretreatment body mass index (BMI) were at substantially lower risk—of suicidal ideation. Efavirenz is now recommended by the World Health Organization for use as a third drug in antiretroviral regimens for use in countries with developing economies; thus, many millions of people are being treated with this drug.
increased risk for cardiovascular disease per unit gain in BMI while taking antiretroviral therapy (Figure 1). Diabetes risk was also substantially increased per unit gain in BMI among patients with a pretreatment BMI of 18.5 kg/m² to 25 kg/m² or 25 kg/m² to 30 kg/m².

**HIV and Hepatitis C Virus Coinfection**

A study in the ICONA (Italian Cohort of Antiretroviral Naive Patients) cohort indicated that higher Fibrosis-4 (FIB-4) score at the start of antiretroviral therapy was associated with increased risk for major liver-related adverse events or death \( (P < .001 \) for FIB-4 score > 3.25) among patients with HIV/hepatitis C virus (HCV) coinfection (Figure 2); major liver-related adverse events were decompensated cirrhosis, hepatic encephalopathy, gastrointestinal bleeding, hepatocellular carcinoma, and hepatorenal syndrome. These findings support the importance of assessment of liver fibrosis in HIV/HCV-coinfected patients. Analysis from another study suggested that higher FIB-4 score at the start of antiretroviral therapy also predicted an increased risk for liver-related adverse events among HIV-monoinfected patients.

Findings thus far in the TURQUOISE-I study suggest that HCV treatment outcomes with current regimens are not impaired by HIV/HCV coinfection. Among patients receiving 12 weeks \( (n = 31) \) or 24 weeks \( (n = 32) \) of the investigational nonstructural protein 5A inhibitor ombitasvir (formerly ABT-267) plus the investigational protease inhibitor paritaprevir/r (formerly ABT-450/r) combined with the investigational nonnucleoside polymerase inhibitor dasabuvir (formerly ABT-333) and ribavirin, HCV virologic response rates were 100% and 100%, respectively, at 4 weeks of treatment (rapid virologic response); 97% and 97%, respectively, at end of treatment (sustained virologic response 4 weeks after end of treatment \( \text{SVR4} \)); and 93.5% in the 12-week group at 12 weeks after end of treatment \( \text{SVR12} \). In another study of 38 patients with history of injection drug use who received methadone or buprenorphine, the same regimen produced end-of-treatment, \( \text{SVR4} \), \( \text{SVR12} \), and \( \text{SVR24} \) rates of 97% each.

**Tuberculosis**

Considerable progress has been made in battling the overlapping HIV and tuberculosis (TB) epidemics, resulting in a greater than 40% decline in HIV/TB coinfection–related deaths and more than 1.3 million lives saved between 2004 and 2012 (Figure 3). However, much work remains to be done. Globally, HIV serostatus was known for only 40% of patients with TB infection as of 2011; although efforts have increased this percentage to approximately 70% in Africa, the percentage remains low in other resource-limited regions around the world, at approximately 30%. Improvements in diagnosis of TB and HIV infections, timeliness of TB and HIV treatment initiation, completion of TB treatment courses, and transitioning TB-infected patients to HIV care are needed.

**In Closing**

Of course, the 20th International AIDS Conference was clouded by the tragic loss of life on Malaysia Airways Flight 17, including that of the former President of the International AIDS Society, Dr Joep Lange. An amazing leader in the field of HIV/AIDS medicine, a mentor to many, and a close friend and colleague, Dr Lange was remembered, along with his partner Jacqueline van Tongeren and others on the flight, throughout the Conference. In the end, the hope represented by the scientific progress evident at the Conference was the best response to the senseless tragedy that affected all.

Presented by Dr Volberding in August 2014. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Volberding in November 2014.

Financial affiliations in the past 12 months: Dr Volberding has served on scientific advisory boards for Bristol-Myers Squibb and Gilead Sciences, Inc.

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Sexually transmitted infections are a resurgent problem in HIV disease. The number of new cases of syphilis among men who have sex with men has continued to increase, requiring renewed vigilance in screening, diagnosis, and treatment. Drug-resistant gonorrhea has prompted changes in treatment regimens and warrants continued monitoring. This article summarizes an IAS–USA continuing education webinar presented by Jeanne M. Marrazzo, MD, MPH, in January 2014.

**Keywords:** HIV, STI, sexually transmitted infection, syphilis, gonorrhea, cephalosporins, antibiotic resistance, hepatitis C virus, HCV, anal dysplasia

Sexually transmitted infection (STI) acquisition and risk-taking behavior are ongoing among some HIV-infected patients in primary care. Data reported in 2012 from a prospective cohort study of 557 HIV-infected adults in primary care in 4 US cities showed that 15% had STIs at time of enrollment and 7% had an incident STI within 6 months of enrollment. Excluding trichomoniasis, 94% of the incident STIs were among men who have sex with men (MSM), with 20% of MSM diagnosed with an STI within 6 months. The most common infections in men were rectal chlamydial infection and oropharyngeal gonorrhea. Risk factors for infection included polysubstance use and having more than 4 sexual partners within 6 months.

**New Syphilis Epidemic**

Data from the Centers for Disease Control and Prevention (CDC) for the period from 2007 to 2013 showed that although the annual number of new cases of primary and secondary syphilis remained steady or declined among women and among men who have sex exclusively with women, it increased by 7% among MSM from 2012 to 2013.²

The presentation of syphilis can be particularly diverse in the context of HIV infection. Findings have included lues maligna, a very invasive skin disorder, and increased frequency of clinically significant symptomatic neuroinvasive disease, especially auditory or ocular neuropathy.

The latent stage of syphilis is characterized by positive treponemal serology in the absence of clinical manifestations, with early (seroconversion within 1 year of infection) and late (seroconversion after 1 year) latency periods characterized by evidence of seroconversion. Approximately two-thirds of individuals with untreated syphilis remain in the latent stage for life.

**Screening**

Traditionally, syphilis screening involved nontreponemal tests, such as the rapid plasma reagin (RPR) and venereal disease research laboratory (VDRL) assays. These tests provide quantitative results that can be followed over time to assess treatment response. Findings would then be confirmed by qualitative treponemal testing with, for example, a Treponema pallidum particle agglutination or a fluorrescent treponemal antibody assay. This traditional screening approach is being replaced by reverse screening, in which qualitative treponemal testing is performed first with enzyme, chemiluminescence, or microbead immunoassays—automated tests that are easier to perform—and then followed by quantitative RPR or VDRL testing. This reverse sequence screening algorithm for syphilis is shown in Figure 2.³

**Neurosyphilis**

Neurosyphilis can occur at any stage of syphilis. Central nervous system (CNS) invasion occurs early in syphilis infection in approximately 30% to 40% of cases and is asymptomatic in the majority of patients. Early symptomatic
forms of neurosyphilis, which may occur within months or years of infection, include acute syphilitic meningitis with neuropathy of auditory, optic, and facial nerves (cranial nerves VI, VII, and VIII); meningo-vascular stroke (stuttering stroke); and altered mental status. CNS gummas have been observed earlier in the brains of HIV-infected patients with syphilis than in the brains of HIV-uninfected patients with syphilis. Later symptomatic presentations of neurosyphilis (eg, occurring after 2 years) include general paralysis and tabes dorsalis. Ocular syphilis can manifest as posterior chamber uveitis, retinitis, or retinal detachment.

There are data indicating that CNS invasion is more likely to occur among HIV-infected patients with CD4+ cell counts of 350/µL or lower or RPR titers of 1:32 or higher. However, there are no data supporting better outcomes of neurosyphilis treatment among such patients in the absence of neurologic symptoms. Thus, lumbar puncture for cerebrospinal fluid (CSF) collection is not recommended in the absence of neurologic symptoms. Patients should be carefully evaluated for neurologic, ophthalmic, and otologic symptoms, and lumbar punctures should be performed for those who are symptomatic.

A CSF VDRL test, the only diagnostic test approved for use on CSF specimens, is highly specific but relatively insensitive in diagnosis. Among HIV-infected patients with neurologic symptoms and negative CSF VDRL test results, treatment can be considered for pleocytosis of greater than 20 white blood cells/µL (a higher threshold than for HIV-uninfected patients, as HIV infection itself is associated with CSF inflammation). The CSF fluorescent treponemal antibody test is not highly sensitive but is specific; a negative test result may help to rule out neurosyphilis, although it should not rule out infection if clinical suspicion is high.

**Treatment**

Syphilis treatment has remained largely unchanged for decades. For primary, secondary, and early latent syphilis, recommended treatment is a single intramuscular (IM) dose of long-acting benzathine benzylpenicillin 2.4 million U. Other penicillin formulations or azithromycin should not be used. Doxycycline 100 mg taken orally twice daily for 14 days may be used but is inferior to benzathine benzylpenicillin. Intravenous or IM ceftriaxone 1 g taken daily for 8 days to 10 days may be used as an alternative treatment to doxycycline but is a challenging regimen to administer, given that it involves the daily injection of a drug that requires refrigeration at a clinic and that the IM injection can be painful. For late latent syphilis, standard treatment is 3 weekly doses of IM benzathine benzylpenicillin 2.4 million U; a 28-day, oral doxycycline regimen is an inferior alternative. For neurosyphilis, standard treatments are aqueous penicillin G 18 million to 24 million U daily for 10 days to 14 days, or procaine penicillin G 2.4 million U plus oral probenicid 500 mg daily for 10 days to 14 days. Daily intravenous ceftriaxone 2 g for 10 days to 14 days may be used as an alternative.

**Gonorrhea**

There has been an increasing number of reports of clinical *Neisseria gonorrhoeae* isolates with resistance to cephalosporins, including reports of patients with gonorrhea resistant to extended-spectrum parenteral agents.

The Gonococcal Isolate Surveillance Project (GISP), a collaborative project of the CDC, monitors trends in gonococcal antibiotic susceptibility among men attending STI clinics. Urethral antibiotic isolates are obtained from the first 25 men per site each month and susceptibility testing is conducted by 5 regional laboratories, with confirmatory testing.
conducted by the CDC. As shown in Figure 3, data from GISP indicate that the percentage of isolates with elevated minimum inhibitory concentrations (MICs) of cefixime has increased steadily in the western United States and among MSM.\textsuperscript{11} In 2010 and 2011, approximately 1.4% of isolates had resistance to cefixime, with the percentage decreasing to approximately 1% in 2012.

There has also been an increase in the percentage of isolates with elevated MICs of ceftriaxone, although the percentage of resistant isolates is not as high as seen with cefixime. Steady increases to 0.3% in 2010 and 0.4% in 2011 were followed by a decline to below 0.3% in 2012. It remains to be seen whether the recent declines in prevalence of isolates resistant to these agents indicate beneficial trends. GISP data indicate that the problem with cephalosporin resistance is occurring largely among MSM. Data from 2005 to 2010 indicated isolates with elevated MICs of cefixime and ceftriaxone in 1.7% and 0.4%, respectively, of 8117 MSM and in 0.2% and 0.1%, respectively, of 26,483 men who have sex exclusively with women.\textsuperscript{12}

**Treatment**

For uncomplicated gonorrhreal infections of the cervix, urethra, or rectum, recommended treatment is a single IM dose of ceftriaxone 250 mg plus either azithromycin 1 g or doxycycline 100 mg twice daily for 7 days. Azithromycin is the preferred choice and should be used in this setting irrespective of whether a patient has chlamydial infection, for which it is also indicated. If there is absolutely no way to administer IM ceftriaxone, a single dose of oral cefixime 400 mg may be used with azithromycin or doxycycline. It is also recommended that IM ceftriaxone 250 mg be used for pharyngeal infections, which are notoriously difficult to eradicate. Vigilance should be maintained for gonococcal persistence.

In cases of treatment failure, an infectious diseases specialist should be consulted, culture and susceptibility testing performed, treatment with IM ceftriaxone (250 mg) plus azithromycin (2 g) attempted, partner treatment ensured, testing for cure completed 1 week after treatment, and the case should be reported to the CDC via state or local public health departments. Unfortunately, there have been at least 2 case reports of treatment failure with gonococcal isolates with high-level resistance to azithromycin, a situation that must be closely monitored.\textsuperscript{13}

It is now recommended that a test of cure, by culture or nucleic acid amplification test (NAAT), be performed in patients not receiving a ceftriaxone regimen.\textsuperscript{14} Although testing is recommended at 7 days after treatment, there are few data on the likelihood of negative NAAT results at 7 days with adequately treated infection. It is therefore reasonable to wait until 10 days after treatment to complete an NAAT.

Recent reports on new treatments have included good results with the aminoglycoside gentamicin or the quinolone gemifloxacin in combination with azithromycin 2 g.\textsuperscript{15} New agents under investigation include solithromycin, dalbavancin, MUT056399 (an inhibitor of fatty acid biosynthesis enzyme), pleuromutilins, bicyclolides, ketolides, nonquinolone topoisomerase inhibitors, and host defense peptides with direct or indirect antibacterial activity. New targets under investigation include gonococcal lipid A and efflux pumps.

The United Kingdom now recommends ceftriaxone 500 mg (rather than the 250 mg dose used in the United States) plus azithromycin instead of cefixime. This change appears to have been accompanied by a reduction in the percentage of isolates with cefixime resistance, from 17.1% in 2010 to 10.8% in 2011.\textsuperscript{16} Whether this indicates a causal relationship remains to be determined.

**Screening**

Annual screening for rectal gonorrhea is important for patients who report engaging in receptive anal sex (regardless of whether they report condom use), particularly because rectal gonorrhea is associated with increased HIV shedding. Similarly, annual screening for pharyngeal infection should be performed for patients who report

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**Figure 2.** Reverse sequence screening algorithm for syphilis infection. CIA indicates chemiluminescence immunoassay; EIA, enzyme immunoassay. Adapted from Centers for Disease Control and Prevention.\textsuperscript{3}

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**Figure 3.** Percentage of gonococcal isolates with elevated minimal inhibitory concentrations (MICs) of cefixime ($\geq 0.25 \mu g/mL$), by US region or by sexual risk behavior, from 2005 to 2011. Testing was not performed in 2007 or 2008, therefore, data for this time period are unavailable. Adapted from Bolan et al.\textsuperscript{11}
engaging in receptive oral sex, as pharyngeal infection appears to offer the opportunity for gonorrhea to acquire mutations from other Neisseria species, which can result in reduced drug susceptibility.

Other STIs

Hepatitis C Virus

There has been an increase in incidence of hepatitis C virus (HCV) infection among MSM, beginning in approximately 2004 and accelerating in recent years.17 Risk factors include unprotected receptive anal intercourse and rough or poorly lubricated, unprotected anal penetration. Current guidelines recommend HCV testing for all HIV-infected patients, injection drug users, and anyone born between 1945 and 1965. Acute infection may be HCV antibody negative. HCV RNA level should be tested in patients with new, unexplained transaminase elevation.

Anal Dysplasia and Cancer

Primary care guidelines from the HIV Medicine Association of the Infectious Diseases Society of America recommend anal Papanicolaou (Pap) testing for patients with a history of receptive anal intercourse, abnormal cervical Pap results, or genital warts.18 Patients with abnormal anal Pap results should be evaluated with high-resolution anoscopy. Human papillomavirus (HPV) DNA screening is not recommended, and its role remains undefined. HPV vaccination is safe and immunogenic for HIV-infected patients and has been shown to prevent anal cancer and anal intraepithelial neoplasia. The introduction of HPV vaccination has resulted in declines in the prevalence of vaccine and nonvaccine high-risk HPV types among young women in the United States and a decline in the prevalence of genital warts in Australia among younger age groups.19,20

Conclusions

HIV-infected patients should be screened for syphilis, gonorrhea, and chlamydia infections at entry to care and periodically thereafter, depending on risk. Rectal testing for gonorrhea and chlamydia infections should be performed for patients who report engaging in receptive anal sex, and oral testing for gonorrhea should be performed in those who report engaging in receptive oral sex. Rescreening for chlamydial and gonococcal infections should be performed 3 months to 6 months after an initial positive test result.

Practitioners should be aware of enzyme immunoassays for syphilis detection and how to use them and should be able to recognize neuroinvasive disease. Vigilance should be maintained when gonorrhea is antibiotic resistant. Patients should receive HPV vaccination but should also continue to undergo Pap screening.

Presented by Dr Marrazzo in January 2014.
First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Marrazzo in December 2014.

Financial affiliations in the past 12 months: Dr Marrazzo has served as an advisor or consultant to AstraZeneca.

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Perspective
HIV Prevention: Integrating Biomedical and Behavioral Interventions

Recommendations for HIV prevention in clinical care settings by an IAS–USA panel were recently published. They include recommendations on HIV testing, antiretroviral therapy initiation, risk-reduction counseling, and antiretroviral therapy adherence counseling for HIV-infected individuals. For individuals at risk for HIV infection, recommendations for preexposure prophylaxis, other risk-reduction strategies, adherence counseling, and postexposure prophylaxis are included. Many HIV-infected individuals in the United States are not fully engaged in HIV care and are not virologically suppressed, thus a crucial component of efforts to reduce HIV transmission is moving patients through the HIV care continuum. This article summarizes an IAS–USA continuing education webinar presented by Carlos del Rio, MD, in September 2014.

Keywords: HIV, prevention, antiretroviral therapy, preexposure prophylaxis, PrEP, postexposure prophylaxis, PEP, HIV testing, adherence, HIV care continuum

In 2012, there were approximately 2.3 million new HIV infections worldwide, including approximately 50,000 new infections in the United States.1 Clinicians play a crucial role in implementing HIV prevention interventions, from HIV testing to ensuring that persons on antiretroviral therapy are virologically suppressed. The IAS–USA HIV Prevention Recommendations Panel recently published recommendations for the biomedical and behavioral prevention of HIV infection in clinical care settings.1 These recommendations seek to consolidate best practices for clinicians for a range of HIV prevention issues.

Data from the Centers for Disease Control and Prevention (CDC) for 2010 indicate approximately 38,000 (range 33,400-42,600) new HIV infections in adult and adolescent men (80% of total) and approximately 9500 (range 8100-10,900) new infections in adult and adolescent women.2 The number of new HIV infections in the United States has remained stable for the past decade, but there have been major changes in specific transmission categories. Between 2002 and 2011, the number of infections decreased in most transmission categories, including among all those who were not men who have sex with men (MSM; 47% reduction), heterosexual women (56% reduction), heterosexual men (35% reduction), injection drug users (69% reduction among women and 65% reduction among men), and MSM who were also injection drug users (58% reduction). The number of infections remained stable among MSM overall, but increased by 132% among MSM aged 13 years to 24 years (Figure 1).3 CDC data for the period of 2008 to 2010 indicate that the greatest numbers of new infections were among blacks, followed by whites and Hispanics, and among MSM (25,000-30,000 cases per year; 12% increase during this period).2

Recommendations for HIV Testing

Knowledge of HIV serostatus is the pivotal step in directing interventions to prevent HIV infection. Approximately 50% of people infected with HIV worldwide are unaware of their serostatus.4 In the United States, HIV-infected individuals who are unaware of their serostatus are accountable for 45% of new infections.5 IAS–USA HIV Prevention Recommendations for HIV testing with regard to HIV prevention efforts are listed in Table 1.1

Prevention Measures for HIV-Infected Individuals

Suppression of infectious HIV RNA in blood and genital secretions through effective antiretroviral therapy reduces the risk of ongoing HIV transmission. The President’s Emergency Plan for AIDS Relief and the World Health Organization (WHO) now recommend antiretroviral treatment for HIV-serodiscordant partners regardless of CD4+ cell count.6,7 For other HIV-infected individuals, WHO now recommends initiating therapy at CD4+ cell counts of 500/µL or less, regardless of symptoms, and at CD4+ cell counts

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Dr del Rio is Professor of Global Health at Rollins School of Public Health and Professor of Medicine at Emory University School of Medicine in Atlanta, Georgia.
greater than 500/µL in some specific clinical settings. In the United States, IAS–USA and Department of Health and Human Services antiretroviral treatment guidelines recommend that antiretroviral treatment be offered to all HIV-infected individuals, regardless of CD4+ cell count, who are ready and willing to initiate and adhere to long-term antiretroviral therapy.

Data on HIV-serodiscordant couples, including that presented in a classic study by Quinn and colleagues of couples in Uganda (Figure 2), show a greater risk of HIV transmission (man to woman or woman to man) when the HIV-1 viral load in the HIV-infected individual is high and a reduced risk of HIV transmission at lower HIV-1 viral loads. Analysis of several cohort studies showed that taking effective antiretroviral therapy reduced the risk of HIV transmission by 66% (rate ratio, 0.34; 95% confidence interval, 0.13-0.92). The strongest and most direct evidence of the effect of antiretroviral therapy in reducing HIV transmission came from the HIV Prevention Trials Network (HPTN) 052 trial, a double-blind, placebo-controlled trial in which 1763 HIV-serodiscordant couples (the HIV-infected partners had CD4+ cell counts of 350/µL-550/µL) were randomized to receive immediate or delayed antiretroviral therapy. Of 29 linked transmission events, 28 occurred in the delayed-treatment group, yielding a relative risk reduction of transmission of 96% with immediate antiretroviral therapy initiation.

A recent analysis outside the clinical trial setting showed an estimated HIV transmission rate of 0% with condoms: sex among heterosexual or same-sex couples in which the HIV-infected partner was taking effective antiretroviral therapy and had a plasma HIV RNA level of less than 200 copies/mL. This analysis included vaginal sex with ejaculation among couples in which the man was HIV-infected (192 couple-years of follow-up [CYFU]), vaginal sex among couples in which the woman was HIV-infected (272 CYFU), receptive anal sex with ejaculation (53 CYFU) and without ejaculation (157 CYFU) among MSM, and insertive anal sex among MSM (262 CYFU). However, there is still uncertainty regarding the upper bounds of the 95% confidence intervals for the

### Table 1. IAS–USA HIV Prevention Recommendations for HIV Testing, Antiretroviral Therapy, and Risk Reduction

<table>
<thead>
<tr>
<th>HIV Testing</th>
<th>Antiretroviral Therapy</th>
<th>Risk Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Adults and adolescents between 15-65 years should be offered HIV testing at least once</td>
<td>• Clinicians should provide education about the personal and public health benefits of antiretroviral therapy and assess patients’ readiness to initiate and adhere to long-term antiretroviral therapy</td>
<td>• HIV-infected individuals should have regular assessment of sexual and injection drug use practices</td>
</tr>
<tr>
<td>• High-risk individuals should be tested more frequently, as appropriate</td>
<td>• Antiretroviral therapy should be offered to patients on diagnosis of HIV infection</td>
<td>• Sexually transmitted infection screening, condoms, and harm-reduction services should be provided to injection drug users (IDUs) in conjunction with adherence strategies</td>
</tr>
<tr>
<td>• Individuals should be informed prior to HIV testing; however, pretest counseling should be sufficient only to meet the individual’s needs and to comply with local regulations.</td>
<td>• Adherence strategies should be developed according to individual patient needs</td>
<td>• Assistance should be provided for patient- or clinician-based notification of sex and IDU partners to facilitate HIV testing and linkage to care, and patients should be encouraged to disclose HIV infection to relevant partners and persons</td>
</tr>
<tr>
<td>• Persons at risk with a negative HIV test result should be informed about the possibility of having a false-negative test result during the HIV infection “window period” and should be encouraged to undergo repeat HIV testing</td>
<td>• Patients should be monitored for nonspecific presentation of acute HIV infection, and diagnostic testing (ie, for plasma HIV RNA level) should be pursued if acute infection is suspected</td>
<td>• IDUs should be provided access to antiretroviral therapy, needle and syringe exchange programs, supervised injection sites, medicalized heroin, and medically assisted therapy (eg, opioid-substitution therapy)</td>
</tr>
<tr>
<td>• Risk-reduction counseling is warranted for people with negative HIV test results who are in high-risk populations (eg, individuals in HIV-serodiscordant sexual relationships)</td>
<td>• Rapid HIV testing should be prioritized for individuals who are less likely to return at a later date for their results</td>
<td>• Individuals who use substances in ways other than injection should be offered antiretroviral therapy, adherence support, and behavioral counseling</td>
</tr>
<tr>
<td>• HIV tests with the best sensitivity and specificity should be used</td>
<td>• HIV self-testing and home testing should be considered for those with recurrent risk or who have difficulties with testing in clinical settings</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Marrazzo et al.¹

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**Figure 2.** Plasma HIV RNA levels and HIV infection rates among HIV-serodiscordant couples in Uganda. Adapted from Quinn et al.²
risk estimates, particularly for receptive anal sex with ejaculation. Additional follow-up is needed to provide more precise risk estimates. Of note, duration of prior antiretroviral therapy without HIV transmission of patients included in this analysis may have selected for lowest-risk HIV-serodiscordant couples.

The IAS–USA HIV Prevention Recommendations for HIV antiretroviral therapy and risk-reduction interventions are listed in Table 1.1

### Prevention Measures for Individuals at Risk for HIV Infection

#### Preexposure Prophylaxis

Several randomized, double-blind, placebo-controlled studies have investigated the efficacy of antiretroviral pre-exposure prophylaxis (PrEP) in preventing HIV transmission. In the iPrEx (Chemoprophylaxis for HIV Prevention in Men) trial of 2499 HIV-seronegative MSM and transgender women in South America, Africa, and southeast Asia, there were 64 HIV infections among 1248 placebo recipients and 36 HIV infections among 1251 patients receiving a fixed-dose combination of tenofovir and emtricitabine (44% preventive efficacy).14 In the Partners PrEP trial of 4758 heterosexual HIV-serodiscordant couples in Africa, in which the HIV-infected partners were not taking antiretroviral therapy and had CD4+ cell counts greater than 495/µL, 52 HIV infections occurred among 1584 couples in the placebo group, 17 HIV infections among 1584 couples in which the HIV-uninfected partner received tenofovir, and 13 HIV infections among 1579 couples in which the HIV-uninfected partner received tenofovir and emtricitabine (67% efficacy with tenofovir; 75% efficacy with tenofovir and emtricitabine).15 In the TDF2 trial of 1219 heterosexual men and women in Botswana, 24 HIV infections occurred among 608 placebo recipients and 9 HIV infections occurred among 611 tenofovir and emtricitabine recipients (62% efficacy).16 In the Bangkok Tenofovir Study of 2413 injection drug users, there were 33 HIV infections among 1209 placebo recipients and 17 HIV infections among 1204 tenofovir recipients (49% efficacy).17

In contrast, in the FEM-PrEP (Pre-exposure Prophylaxis Trial for HIV Prevention among African Women) trial of 2120 heterosexual women in Kenya and South Africa, 35 HIV infections occurred among 1058 placebo recipients and 53 HIV infections among 1062 patients receiving tenofovir and emtricitabine; the trial was stopped for futility.18 In the VOICE (Vaginal and Oral Interventions to Control the Epidemic) trial, 5029 heterosexual women in Uganda, Zimbabwe, and South Africa received tenofovir and emtricitabine, tenofovir tablets, or placebo and were randomized to receive tenofovir gel or placebo. The comparison of tenofovir tablets and gel was stopped for futility, and tenofovir and emtricitabine exhibited no preventive efficacy.19

The difference in PrEP efficacy in these trials can be explained by differences in patient adherence to the assigned medication. The 44% preventive efficacy rate in the iPrEx trial was observed in the context of a 51% adherence rate to the prophylactic regimen. The 75% efficacy rate in the Partners PrEP trial occurred in the context of an 82% adherence rate. The 6% efficacy rate in the FEM-PrEP trial occurred in the context of a less than 40% adherence rate. However, there are important discrepancies between measures of adherence and drug detection. In the iPrEx trial, among those reporting perfect adherence, 51% had detectable drug levels, but this varied by site, with higher correlations between adherence measures in the United States and lower correlations between adherence measures in the Andean region of South America.20 In the open-label extension of the iPrEx trial, the HIV incidence rate was 4.7 per 100 person-years among those with no detectable drug levels in dried blood spots, 2.3 per 100 person-years if the drug concentrations suggested use of fewer than 2 tablets per week, 0.6 per 100 person-years for those who used 2 to 3 tablets per week, and 0.0 per 100 person-years for those who used 4 or more tablets per week.21,22

IAS–USA HIV Prevention Recommendations for PrEP are listed in Table 2.1 CDC guidance on PrEP recommends prescribing a once-daily tablet of tenofovir and emtricitabine after a negative HIV antibody test result is obtained.23,24 Further, acute HIV infection should

### Table 2. IAS–USA HIV Prevention Recommendations for PrEP and PEP

<table>
<thead>
<tr>
<th>Preexposure Prophylaxis (PrEP)</th>
<th>Postexposure Prophylaxis (PEP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Daily tenofovir and emtricitabine as PrEP should be offered to:</td>
<td>• PEP should be offered as soon as possible, within 72 hours, to all individuals who have sustained a mucosal or parenteral exposure to HIV</td>
</tr>
<tr>
<td>- Individuals at high risk for HIV infection based on background incidence (&gt;2%) or recent diagnosis of sexually transmitted infection (especially syphilis, gonorrhea, or chlamydia)</td>
<td>• The US Public Health Service preferred PEP regimen, currently tenofovir and emtricitabine with raltegravir, should be used</td>
</tr>
<tr>
<td>- Individuals who have taken PEP more than twice in the past year</td>
<td>• Women who are prescribed PEP should also be offered emergency contraception to prevent pregnancy</td>
</tr>
<tr>
<td>- Injection drug users who share injection equipment, inject 1 or more times per day, or inject cocaine or methamphetamines</td>
<td>• Individuals who are prescribed PEP should be rescreened for HIV infection with a fourth-generation HIV antigen and antibody test 3 months after completion of the treatment course</td>
</tr>
<tr>
<td>• PrEP should be part of an integrated risk-reduction strategy and may become unnecessary with behavioral changes. Patient risk should be regularly assessed and PrEP discontinuation considered if behavioral modifications (ie, reduction in high-risk sexual or injection drug use practices) have been made</td>
<td></td>
</tr>
<tr>
<td>• PrEP considerations for HIV-serodiscordant couples should include whether the HIV-infected partner is taking antiretroviral therapy, the HIV-uninfected partner’s access to care, and associated costs</td>
<td>Adapted from Marrazzo et al.1</td>
</tr>
</tbody>
</table>

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be ruled out with HIV-1 RNA testing if there are suggestive or nonspecific symptoms, patients should receive counseling regarding safer sexual practices, pregnancy should be ruled out for women, patients should be screened for hepatitis B virus infection, and creatinine clearance should be greater than 60 mL/min. A 90-day supply of tenofovir and emtricitabine should be given and a follow-up HIV test and assessment of adherence performed before refill. Monitoring for sexually transmitted infections (STIs) should be performed every 6 months and blood urea nitrogen and serum creatinine levels should be assessed every 12 months.

There are several concerns with PrEP that must be addressed with longer follow-up periods and continued study. Risk compensation has thus far not been observed in clinical trials. Renal insufficiency has been rare and reversible, although individuals were required to have normal renal function to participate in clinical trials. Statistically but not clinically significant bone demineralization has been observed after 18 months of PrEP; additional follow-up is needed to determine whether bone demineralization becomes of clinical importance. Transmission of resistance has thus far been observed only in patients taking PrEP who had acute HIV infection and were therefore receiving inadequate antiretroviral therapy. All but 1 case of HIV transmission involved the M184V resistance mutation.

**Postexposure Prophylaxis**

Occupational postexposure prophylaxis (PEP) is recommended for health care workers who have been exposed to HIV-infected material via needlesticks or cuts. Nonoccupational PEP, for sexual or other exposures, is administered to those who have had mucosal contact with an HIV-infected individual’s blood or genital secretions. IAS–USA HIV Prevention Recommendations for PEP are listed in Table 2.

**HIV Prevention Efforts in Clinical Care**

Improvement in moving patients through the continuum of HIV care and increasing efforts in risk assessment, risk reduction, and screening for and treatment of STIs are crucial to HIV prevention. IAS–USA HIV Prevention Recommendations for STI screening and treatment, as well as reproductive health and hormonal contraception, are listed in Table 3.

The CDC estimates that in 2011 there were approximately 1.2 million persons with HIV disease in the United States, 86% were diagnosed, 40% were engaged in care, 37% were prescribed antiretroviral therapy, and 30% achieved virologic suppression. Given that effective antiretroviral therapy substantially reduces transmission risk, there is enormous room for improving all stages of the HIV continuum of care and ultimately increasing the percentage of people living with HIV who achieve sustained virologic suppression. IAS–USA HIV Prevention Recommendations for improving linkage to HIV care are listed in Table 3.1

**Summary**

After 30 years, an AIDS-free generation seems possible. However, the involvement of clinicians is paramount to achieve this goal. All adults and adolescents should be offered HIV testing. For all persons with or at risk for HIV infection, injection drug use and sexual risk practices should be regularly assessed. Antiretroviral therapy and adherence support should be offered to all individuals with confirmed HIV infection, and PrEP and adherence support should be offered to those at risk for HIV infection. A high index of suspicion should be maintained for nonspecific

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### Table 3. IAS–USA HIV Prevention Recommendations for Sexually Transmitted Infection Screening, Linkage to HIV Care, and Reproductive Health and Hormonal Contraception

<table>
<thead>
<tr>
<th>Sexually Transmitted Infection Screening</th>
<th>Linkage to HIV Care</th>
<th>Reproductive Health and Hormonal Contraception</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Regular screening for common sexually transmitted infections should be performed based on sexual history</td>
<td>• Linkage to HIV care should be actively facilitated as soon as possible following a new diagnosis of HIV infection</td>
<td>• Currently, data are not sufficiently conclusive to restrict use of any hormonal contraception method</td>
</tr>
<tr>
<td>• HIV-infected individuals should be tested for hepatitis C virus at entry to care and reassessed at regular intervals</td>
<td>• Case management interventions utilizing individual patients’ personal strengths should be incorporated to promote linkage to and retention in HIV care</td>
<td>• Women using injectable progestin-only contraception should also be advised to always use condoms and to use other HIV preventive measures as feasible</td>
</tr>
<tr>
<td>• Quadrivalent human papillomavirus vaccination should be offered to all HIV-infected individuals who meet Advisory Committee for Immunization Practices criteria</td>
<td>• Patient support services should be employed, including assistance with patient health navigation, community and peer outreach, culturally appropriate print media, verbal encouragement from clinic staff promoting health care utilization and retention, and youth-focused case management and support where appropriate</td>
<td>• Counseling with regard to the range of options for family planning, including hormonal contraception, should be offered to HIV-infected women</td>
</tr>
<tr>
<td>• HIV-infected individuals who have not already been infected with hepatitis B virus (HBV) should be offered HBV vaccination</td>
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<td></td>
</tr>
<tr>
<td>• Routine herpes simplex virus 2 (HSV-2) infection screening should be considered for HIV-infected individuals who do not know their HSV-2 serostatus considering suppressive antiviral therapy to prevent HSV-2 transmission</td>
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</tr>
</tbody>
</table>

Adapted from Marrazzo et al.1
presentation of symptomatic acute HIV infection. Linkage to HIV care should be emphasized and supported. Finally, individualized risk-reduction counseling should be facilitated and regular STI screening should be performed.


Financial affiliations in the past 12 months: Dr del Rio has no relevant financial affiliations.

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Harjot K. Singh, MD, ScM, and Eugenia Siegler, MD

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Stuart C. Ray, MD, Justin R. Bailey, MD, PhD
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Habib Ramadhani Omari, MD, MPH, MHS, and John A. Bartlett, MD
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Antiretroviral therapy has been tremendously successful in reducing morbidity and mortality among HIV-infected persons, and an estimated 10,000,000 people globally are now receiving it. Stigma and the need for strict medication adherence are commonly encountered throughout the world. In resource-limited contexts, there is an additional challenge of maintaining a continuous drug supply and having the ability to properly monitor treatment. Early treatment initiation is essential to preserve immunity, prevent the emergence of AIDS-defining illnesses, and decrease HIV transmission.

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Jonathan Li, MD
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Recommendations for Testing, Managing, and Treating Hepatitis C is a website sponsored by the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) in collaboration with the International Antiviral Society–USA (IAS–USA) to provide the most current guidance for the treatment of hepatitis C virus (HCV).

Recently, several sections of the Guidance were extensively revised based on newly available therapies approved by the US Food and Drug Administration. Visit www.hcvguidelines.org to review the updates to sections on Initial Treatment of HCV Infection; Retreatment of Persons in Whom Prior Therapy Has Failed; Monitoring Patients Who Are Starting Hepatitis C Treatment, Are on Treatment, or Have Completed Therapy; and Unique Populations (Patients With HIV/HCV Coinfection, Patients With Decompensated Cirrhosis, Patients Who Develop Recurrent HCV Infection Post–Liver Transplantation, and Patients With Renal Impairement).

Available sections:
- HCV Testing and Linkage To Care
- When and in Whom to Initiate HCV Therapy
- Initial Treatment of HCV Infection
- Retreatment of Persons in Whom Prior Therapy Has Failed
- Monitoring Patients Who Are Starting Hepatitis C Treatment, Are on Treatment, or Have Completed Therapy
- Unique Patient Populations
  - Patients With HIV/HCV Coinfection
  - Patients With Decompensated Cirrhosis
  - Patients Who Develop Recurrent HCV Infection Post–Liver Transplantation
  - Patients With Renal Impairement
- Management of Acute HCV Infection
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- Annual Improving the Management of HIV Disease® Full-Day Courses
  - Atlanta, Georgia—Tuesday, March 10, 2015
  - San Francisco, California—Friday, March 20, 2015
  - New York, New York—Tuesday, March 31, 2015
  - Los Angeles, California—Wednesday, April 29, 2015
  - Washington, DC—Wednesday, May 13, 2015

- Evolving Strategies in Hepatitis C Virus Management: Small-Group, Intensive, Half-Day Workshops
  - Atlanta, Georgia—Monday, March 9, 2015
  - San Francisco, California—Thursday, March 19, 2015
  - Los Angeles, California—Tuesday, April 28, 2015
  - Washington, DC—Tuesday, May 12, 2015
  - Chicago, Illinois—Tuesday, May 19, 2015

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