Primary Care Reports
The Practical, Peer-Reviewed Journal for Primary Care and Family Physicians
Volume 16, Number 7 / July 2010 www.ahcmedia.com

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Statement of Financial Disclosure

To reveal any potential bias in this publication, and in accordance with Accreditation Council for Continuing Medical Education guidelines, we disclose that Dr. Wise (editor) serves on the speaker's bureau for the Medicines Company Dr. Li (author) receives research support from Bristol Myers Squibb and is a retained consultant for Tibotec. Dr. Sax (author) is a consultant for Abbott, BMS, Gilead, GSK, Merck, Tibotec, and ViiV; he also receives grant support from Gilead, Merck, and Tibotec. Dr. Winslow (peer reviewer) serves on the speaker's bureau for GlaxoSmithKlein and Cubist Pharmaceuticals and is a retained consultant for Siemens Diagnostics. Mr. Underwood (associate publisher), and Ms. Mark (specialty editor) report no relationships with companies related to the field of study covered by this CME activity.

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What the Primary Care Physician Needs to Know About HIV

Although the treatment of HIV disease has become quite complex and typically beyond the scope of most PCPs, PCPs play an important role in the co-management of patients, new diagnoses, and postexposure prophylaxis.
—The Editor

There have been impressive success stories in the field of HIV over the past decade. Most notably, these include the near-elimination of mother-to-child HIV transmission in the United States and the dramatic improvement in survival — both the result of potent combination antiretroviral therapy (ART), which is now standard of care. However, these successes have been accompanied by ongoing challenges. Approximately 1 in 5 people with HIV in the United States is unaware that they carry the virus, but making HIV testing a routine part of medical care remains a controversial strategy. Increased options for HIV therapy bring with them a greater number of potential adverse event profiles and drug-drug interactions, as well as increasingly complex drug resistance profiles. Prolonged survival of patients with HIV has led to an aging population now dealing with the consequences of both long-standing HIV infection and medication-associated toxicities. HIV vaccine studies have demonstrated limited efficacy at best, and thus far standard ART cannot cure this chronic infection.

Because of these complexities, the treatment of HIV infection should be under the direction of an HIV specialist. However, the primary care physician continues to play an important role in the diagnosis of new infections and co-management of the patient with HIV, who will increasingly have non-infectious complications common to an aging general medical population. This article will provide an overview of HIV epidemiology, testing guidelines, key information to be elicited during the history and physical examination, and initial and follow-up laboratory evaluations. In addition, the basic principles of HIV therapy, both for treatment and for prevention, will be reviewed.

Epidemiology of HIV in the United States

As of 2006, approximately 1.1 million individuals were estimated to be living with HIV in the United States.[1] During the earliest years of the epidemic, HIV/AIDS primarily affected white men who have sex with men (MSM). Since then, the burden of disease has broadened to affect an increasing number of women and minorities.[2,3] Despite this change, the majority of new infections still are in men (73%).[2] African Americans account for 45% of new infections; since they are 12% of the U.S. population, they are clearly disproportionately affected by the epidemic. Caucasians make up 35% and Hispanics 17% of new infections. Individuals aged 20-49 years account for the vast majority of new cases. The most common risk factor for transmission is MSM (53%). Heterosexual transmission accounts for 31% of new infections, and intravenous

Executive Summary

- Approximately 1 in 5 people with HIV in the United States are unaware they carry the virus.
- The majority of new infections involve men (73%), with the vast majority in the 20-49 year-old age group.
- It is estimated that an average of 7-9 years have elapsed before most patients are diagnosed.
- Current guidelines recommend starting therapy for those with CD4 counts of < 500 cells/microliter, in pregnant women, patients with HIV-associated nephropathy, and in those with HBV co-infection.
- There are six FDA-approved classes and more than 20 antiretroviral agents and co-formulations available. The linchpins of current strategy in reducing perinatal transmission involve ART both antepartum and intrapartum as well as infant postexposure prophylaxis and avoidance of breast-feeding.

drug users (IDU) account for 12%. While overall incidence of HIV/AIDS leveled off between 1999 and 2006, there were increasing numbers of new infections among MSM in men and through high-risk heterosexual transmission in women, predominantly among racial and ethnic minorities. Certain regions have particularly high HIV prevalence, similar to that seen in sub-Saharan Africa. For example, 1 in 16 black men in Washington, D.C. are infected, and in some urban centers, the prevalence of HIV among MSM is close to 30%.[4]

HIV Testing

Patient Selection. Earlier diagnosis of HIV infection is important not only for optimal clinical outcomes, but also for limiting the spread of the epidemic.[5] However, an estimated 21% of individuals living with HIV in the United States do not know their status.[1] Those who are diagnosed often are found late in their disease. It is estimated that an average of 7-9 years has elapsed before most are diagnosed, and almost 40% of those newly diagnosed with HIV progress to end-stage AIDS within 1 year of the test.[6,7] Early diagnosis of HIV not only improves survival, but those who are aware of their status are less likely to transmit HIV to others.[8] In 2006, these numbers led the Centers for Disease Control (CDC) to recommend routine HIV testing for all individuals aged 13 to 64 years, except those living in areas with extremely low HIV prevalence (<0.1%) who have no sexual contact or other HIV risk factors.[7] The CDC further recommended annual screening for those at high risk for HIV infection — specifically, gay men, injection drug users, and seronegative sexual partners of those known to be HIV-infected. While the American College of Physicians also endorses routine HIV testing,[9] the American Academy of Family Physicians (AAFP) and the U.S. Preventive Services Task Force (USPSTF) continue to recommend testing for those with known risk factors and in high-risk clinical settings (e.g., emergency departments, STD clinics, correctional facilities, homeless shelters, and primary care clinics in high-prevalence areas).[10,11] All guidelines recommend routine HIV testing of pregnant women in the first trimester, as HIV therapy initiated during pregnancy virtually eliminates the risk of transmission of HIV to the newborn. The CDC also recommends a repeat test in the third trimester for women with HIV risk factors and those in high-prevalence settings.[7]

HIV Tests. In order to decrease barriers to testing, the CDC guidelines do not mandate either pre-test counseling or a separate written consent,[7] although providers should be still follow their state and local laws on counseling and consent. The standard test for diagnosis of HIV infection is detection of antibodies by either a rapid HIV test or an enzyme-linked immunoassay (EIA) followed by a confirmatory Western blot or immunoflourescent assay.[12] A number of rapid tests for HIV are FDA-approved and can provide results within 20 minutes: Clearview HIV 1/2 STAT-PAK Assay, Clearview Complete HIV1/2, Multispot HIV-1/HIV-2 Rapid Test, OraQuick Advance Rapid HIV-1/2 Antibody test, Reveal G3 Rapid HIV-1 Antibody Test, and Uni-Gold Recombigen HIV Test. The OraQuick test can be used on both plasma and oral fluid specimens, but is not approved for children younger than 13 years. Screening enzyme immunoassays have been reported to have a 99.7% sensitivity and 98.5% specificity.[13] Given the high sensitivity and slightly lower specificity of screening HIV tests, all positive samples must be confirmed by either a Western blot or indirect immunofluorescence assay; laboratories will do this confirmatory testing following standard EIAs as part of their routine testing procedures. With a confirmatory Western blot, the chance of a false-positive test in a low-prevalence setting is 1 in 250,000.[13] In most cases, a positive screening test and negative or indeterminate Western blot should prompt repeat testing 4 weeks after the initial test, along with measurement of HIV viral load, as in rare circumstances this pattern of HIV antibody testing may occur during HIV seroconversion. Similarly, individuals with HIV risk factors who have signs and symptoms of acute retroviral syndrome (fever, rash, pharyngitis, lymphadenopathy, aseptic meningitis) may present in

the 2- to 8-week window period when antibodies to HIV have not yet fully developed. To avoid false-negative results, these patients should be offered HIV viral RNA testing in addition to serologic testing. If acute HIV infection is present, the HIV RNA level generally will be greater than 500,000 copies/mL. HIV RNA testing should not be generally used for diagnosis of chronic HIV infection since low copy number false-positive results commonly occur.

Primary Care and Prevention of Opportunistic Infections

Initial and Follow-up Evaluations. The initial patient evaluation should include a comprehensive assessment of behavioral risk factors, medical history, physical examination, and a detailed laboratory evaluation.[14] The complete guidelines to the initial evaluation are available from guidelines issued by the Infectious Disease Society of America[12] and the DHHS.[15] Patients living with HIV are often dealing with concurrent social, psychiatric, substance abuse, and medical issues. The initial evaluation should include an assessment of medical and psychiatric comorbidities, high-risk behaviors including substance abuse and sexual history, economic situation (e.g., housing), social support, and the patient's knowledge of HIV. Health care providers also should provide HIV education including HIV risk factors and strategies for preventing HIV transmission to others.

Recommended laboratory testing provides baseline immune and HIV status, as well as organ function and the risks of co-infections. (*See Table 1.*) In general, HIV patients should have a follow-up evaluation every 3-4 months. However, the frequency of follow-up evaluations can vary depending on the immune status of the patient and the rate of immunologic change. In the event of an antiretroviral medication change, safety labs and immunologic/virologic response to therapy should be monitored at earlier intervals (2-4 weeks). The recommended follow-up laboratory and health care maintenance evaluations are also shown in Table 1. In addition to the HIV-specific primary care considerations, HIV-infected patients should undergo many of the same health care screening evaluations as HIV-negative patients, including tests for colorectal, breast, and prostate cancers. Hyperlipidemia should be managed according to the National Cholesterol Education Program guidelines, but lipid-lowering agents must be chosen carefully, as there are significant drug-drug interactions between certain statins and protease inhibitors.[14] For example, simvastatin levels increase significantly when co-administered with HIV protease inhibitors, and hence should not be used; safer choices include rosuvastatin, pravastatin, or low-dose atorvastatin.

Vaccines. Recommended adult vaccinations are listed in Table 2 with differences in those recommended for healthy, HIV-uninfected adults.[16] In general, it is best to avoid live-attenuated intranasal influenza and oral polio vaccines in HIV-positive patients with low CD4 cell counts. Patients with AIDS, CD4 cell count < 200 cells/mL or < 15% should not receive the MMR, varicella, zoster, intranasal influenza, and yellow fever vaccines. As vaccine responses are more robust in patients with higher CD4 cell counts, deferring vaccinations until after initiating ART is recommended in most situations.

Prevention of Opportunistic Infections (OIs). The CD4 T-cell count (or CD4 count) is the main marker of immune function and the primary measure by which HIV disease progression is monitored. During acute HIV infection, there is an initial peak in plasma viral load and drop in the CD4 cell count. The CD4 cell count rebounds around 3-6 months after the primary infection.[17] Without treatment, the CD4 count will generally decline at a rate of 25 to 100 cells/μl per year,[18] with wide variability between patients. As the CD4 cell count declines, patients are at increased risk of OIs, which are the principal causes of morbidity and mortality in advanced HIV disease. The key recommendations for the primary prophylaxis of common OIs are shown in Table 3 and reflect the changing risk based on CD4 cell count, prior exposure, and the geographic distribution of the pathogens. Comprehensive guidelines on the prevention and treatment of HIV-related OIs were updated in 2009.[19] The importance of OI prophylaxis has diminished since the introduction of effective ART, as HIV therapy can in most cases reverse immunosuppresion sufficiently to make specific antimicrobial prophylaxis unnecessary.

Antiretroviral Therapy

When to Start and Why. When to start ART in patients without HIV-related symptoms remains one of the most controversial areas in the clinical care of HIV patients. Since the first antiretroviral agent (ARV) became available more than two decades ago, multiple new medications have been developed, with reduced short- and long-term adverse effects and lower pill burden. When combination ART became widely available in the late 1990s, some advocated a "hit early, hit hard" strategy in the hopes that early treatment could potentially eradicate the infection.[20] During the next few years, the pendulum swung toward delaying therapy as it became apparent that eradication of HIV infection was not possible and that ART would be limited by adverse effects, especially disfigurement due to lipodystrophy, painful peripheral neuropathy, and other effects and leading to a sharply reduced quality of life. In addition, some patients reported that these complex regimens fostered treatment fatigue and suboptimal adherence, eventually leading to drug resistance.

During the past few years, however, there has once again been a shift toward earlier initiation of therapy, even in patients with no symptoms and relatively high CD4 cell counts.[21] Simpler drug regimens,

Table 1: Recommended Initial and Follow-up Laboratory and Health Care Maintenance Evaluation

Category	Test	Comments for initial evaluation	Follow-up intervals
HIV-specific	CD4 cell count and percentage		3-4 months
	Plasma HIV RNA (viral load)		3-4 months
	HIV resistance testing (genotypic)	If HIV RNA > 1,000 copies/mL	Prior to initiating ART or at virologic failure
	HIV serologic testing	Unless previously documented	
Safety tests	CBC, electrolyte, kidney, and liver function tests		3-4 months while on ART or OI prophylaxis
	Urinalysis		
	Fasting glucose and lipid profile		6-12 months and 1-3 months after starting or modifying ART
Co-infection	Syphilis		Annually in patients at risk
	Other STDs	Gonorrhea, Chlamydia, Trichomonas	Annually in patients at risk
	Toxoplasma gondii IgG[1]		
	Tuberculosis	Tuberculin skin test[2] or interferon-γ release assay	Annually in patients at risk
	Viral hepatitis	HBV sAg, sAb, cAb, HCV ab, total HAV Ab	If repeat exposure or elevated LFTs
Situation-specific	Co-receptor tropism assay	Prior to initiation of maraviroc	
	HLAB*5701	Prior to initiating abacavir	
	Glucose-6-phosphate dehydrogenase	Prior to starting dapsone, primaquine, and sulfonamides	
	CMV antibody[3]	For populations at low risk of prior infection (not MSM, IVDU)	
	VZV antibody	If no history of chickenpox, shingles, or vaccination	
	Chest radiograph	If TB screening test positive	Annually in patients at risk
	Serum testosterone level	Men with weight loss, loss of libido, erectile dysfunction, or depressive sxs	
Health care maintenance[4]	Ophthalmologic exam	If CD4 cell count < 50 cells/mL	Annually if CD4 count < 50 cells/mL
	Cervical Pap test		Two in the first year, then annually
	Anal Pap test	Consider for MSM	Consider annually in MSM
	Depression screen		Annually

[1]Individuals with negative Toxoplasma IgG should be counseled about the prevention of infection including properly cooking meat and avoiding cat litter. [2]Positive PPD is defined as 5 mm of induration or greater. [3]Patients who are CMV IgG negative should receive CMV-negative or leukocyte-reduced blood products. [4]Test listed only if guidelines significantly different than in patients without HIV based on the U.S. Preventive Services Task Force.

including the one-pill once-a-day formulation of tenofovir, emtricitabine, and efavirenz (Atripla), have led to improved drug adherence and are associated with fewer side-effects. In addition, there is evidence that antiretroviral treatment reduces morbidity and mortality even at higher CD4 cell counts,[22] likely through the prevention of "non-AIDS" complications such as cardiovascular disease and malignancies. Several studies have

Table 2: Adult Immunizations for HIV-positive Individuals

Vaccine	Comments
Haemophilus influenzae type B	For patients with asplenia or history of *Haemophilus* infection
Hepatitis A	For MSM, injection drug use, HBV or HCV co-infection, chronic liver disease
Hepatitis B	Test for HBV sAb response after vaccination
Human papillomavirus	Same as for patients without HIV
Influenza	Intranasal vaccine contraindicated
Meningococcal	For patients with asplenia, complement deficiencies, college students, and those with potential travel exposure
MMR	Contraindicated for patients with AIDS, CD4 count < 200 cells/mL, or CD4 percent < 15%
Pneumococcal	Not recommended for patients with AIDS, CD4 count< 200 cells/mL, or CD4 % < 15%. Consider booster dose 5 years after immunization.
Polio	Oral vaccine contraindicated
Tetanus toxoid	Same as for patients without HIV
Varicella/Zoster	Contraindicated for patients with AIDS, CD4 count < 200 cells/mL, or CD4 percent < 15%

shown that CD4 counts < 500 cells/µl are associated with increased risk of AIDS-defining and non-AIDS-defining malignancies[23,24] and that ART can decrease inflammation and immune activation thought to contribute to cardiovascular and other complications in HIV-positive patients.[15,25,26] ART also lowers viral load, which decreases the rate of HIV transmission and has important public health implications.[27,28]

Current guidelines issued by the Department of Health and Human Services recommend starting therapy with a CD4 count of ≤ 500 cells/µl, and that treatment can be considered in those with even higher CD4 counts.[15] In addition, ART should be initiated in pregnant women, patients with HIV-associated nephropathy, and those needing treatment for HBV co-infection regardless of CD4 count. Patients initiating therapy should be counseled regarding the risks and benefits of treatment, the importance of adherence, and the likely need for life-long therapy.

Treatment Regimens

There are now six FDA-approved classes and more than 20 antiretroviral agents and co-formulations available. Recommended regimens consist of three active agents from at least two drug classes. Recommended regimens use two nucleoside reverse transcriptase inhibitors (NRTIs) (generally a one-pill daily co-formulation of tenofovir/emtricitabine [Truvada] or abacavir/lamivudine [Epzicom]) with either a non-nucleoside reverse transcriptase inhibitor (NNRTI), a protease-inhibitor (PI), or an integrase inhibitor. Most protease inhibitors are optimally given with low doses of ritonavir, which acts as a pharmacokinetic booster but not as an antiviral; as a result, patients receiving PI-based treatments are usually on 4 drugs, with only three of them given for antiviral activity.

As noted above, one of the most popular HIV regimens is a single pill of co-formulated tenofovir, emtricitabine, and efavirenz. This treatment is not appropriate for all HIV patients, however, including those who have baseline resistance to any of its components due to acquisition of a drug-resistant virus. Because of the efavirenz, which has caused neural tube defects in primates, it is contraindicated in pregnant women during the first trimester or women of childbearing age who do not use reliable birth control. Efavirenz also induces distinctive central nervous system effects that may not be tolerated by some individuals, especially those with severe psychiatric comorbidities, although in controlled trials, worsening of pre-existing psychiatric disease was not observed.

Other "preferred" regimens for treatment-naïve individuals based on DHHS guidelines include the co-formulated tenofovir/emtricitabine in conjunction with either the protease inhibitors ritonavir-boosted atazanavir or ritonavir-boosted darunavir, or the integrase inhibitor raltegravir.[15] These recommendations take into account efficacy as demonstrated in prospective clinical trials, ease of dosing, and safety history. When initiating or changing ART regimens, it is also important to note that many antiretroviral agents, especially the ritonavir-boosted protease inhibitors, have significant interactions with other commonly used drugs such as statins,

Table 3: Prophylaxis for Opportunistic Infections

Organism and Condition	Indication	First-line Treatment
Pneumocystis jirovecii pneumonia (PCP)	CD4 < 200 cells/μL or < 14% or thrush	Trimethoprim-sulfamethoxazole (TMP-SMX) 1 DS or SS PO daily
Toxoplasma gondii encephalitis	CD4< 100 cells/μL and Toxoplasma IgG positive	TMP-SMX 1 DS PO daily
Disseminated *Mycobacterium avium* complex (MAC) disease	CD4 < 50 cells/μL	Azithromycin 1200 mg PO weekly
Histoplasma capsulatum infection	CD4< 100 cells/μL and lives in endemic area	Itraconazole 200 mg PO daily
Coccidiomycosis	CD4 < 250 cells/μL and IgM or IgG positive and lives in endemic area	Fluconazole 400 mg PO daily or Itraconazole 200 mg PO bid
Esophageal candidiasis	Secondary prophylaxis for recurrent disease	Fluconazole
Cryptococcus meningitis	Secondary prophylaxis after initial treatment	Fluconazole
Cytomegalovirus	Secondary prophylaxis after initial treatment for end-organ disease	Valganciclovir
Herpes simplex or varicella zoster	Secondary prophylaxis for recurrent outbreaks	Valacyclovir, famciclovir, or acyclovir

Adapted from DHHS 2009 guidelines[19] and Gallant[14].

anti-seizure medications, psychiatric drugs, treatments for erectile dysfunction, and inhaled corticosteroids.[15]

The goal of ART is to suppress HIV-1 replication and to lower the viral load to undetectable levels (< 50 copies/mL). With a successful regimen, this usually occurs within 3-6 months and is accompanied by a rise in CD4 cell counts.[14] Virologic "blips" are occasional low viral loads (< 500 copies/mL) that do not persist and are usually representative of laboratory artifact (proviral DNA leaking out of cells is falsely measured as RNA in PCR-based viral load assays) or residual virus released from long-lived reservoirs. These "blips" do not constitute virologic treatment failure, which is defined as persistently detectable viremia suggestive of viral replication. Treatment failure is usually indicative of medication nonadherence and/or the presence of drug resistance mutations. With the potency of currently available drugs, by far the most common cause of virologic failure is that the patient has stopped taking the medications. In clinical cohorts today, the vast majority of patients treated for HIV are successfully treated, with only 10-20% experiencing treatment failure.[29]

Resistance Testing

Recent studies have shown that 6-16% of treatment-naïve individuals harbor HIV with drug resistance mutations.[15] This baseline resistance can impair the efficacy of antiretroviral therapy, and hence a resistance test is recommended at the time of HIV diagnosis. The other main indication for resistance testing is at the time of virologic failure. In both settings, the goal of resistance testing is to avoid using drugs with limited or no antiviral activity.

There are currently two main types of drug resistance assays, genotype and phenotype. Genotype assays detect mutations in the virus known to confer resistance to specific antiretroviral agents. Phenotype assays measure the ability of HIV to grow in different concentrations of HIV drugs. While the phenotypic assays are more intuitive (and closer to susceptibility testing done for bacteria), in most situations genotypic testing is preferred. This preference is based on lower cost, wider availability, better sensitivity of detecting mutations present in mixtures, and a faster turnaround time. Phenotype assays are most useful in patients with complex patterns of drug resistance mutations (especially to HIV protease inhibitors) that may be difficult to interpret. In general, interpretation of HIV resistance testing is a skill reserved for clinicians who have extensive experience caring for patients with HIV; the primary care provider's role will usually be to order a genotype test in a newly diagnosed patient or in someone experiencing virologic failure.[12,15]

Metabolic Complications

Antiretroviral therapy has been linked to a number of chronic health conditions including insulin resistance, subcutaneous lipoatrophy, regional fat accumulation, lipid abnormalities, and cardiac disease.[12,30] The multicenter AIDS Cohort Study found a higher risk of insulin resistance with increased exposure to nucleoside reverse transcriptor exposure,[31] while other trials have shown a modest impact of certain protease inhibitors on

insulin sensitivity.[12] The spectrum of HIV lipodystrophy encompasses both fat accumulation (lipohypertrophy) and fat loss (lipo-atrophy).[32] Fat accumulation primarily occurs centrally in the viscera, but can also manifest as enlarged dorsocervical fat pad ("buffalo hump"), chin fat ("horse collar"), or increased breast tissue. Fat loss, on the other hand, generally occurs in the face, extremities, and buttocks. These fatty changes are associated with an increased risk of diabetes, coronary artery disease, hyperlipidemia, and osteoporosis. Both lipodystrophy and hyperlipidemia are most commonly associated with older NRTIs and protease inhibitors no longer in wide use.[32-35] The Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study is a collaboration of 11 prospective cohorts from Europe, Australia, and the United States. Analysis of this combined cohort suggests that several antiretroviral agents (indinavir, ritonavir-boosted lopinavir, ddI, and abacavir) may be associated with increased risk of myocardial infarctions.[36] Given the potential complications of HIV therapy and the likelihood that HIV itself induces increased cardiovascular risk through inflammatory mechanisms, aggressive reduction of traditional CV risk factors is an emerging critical role of the primary care physician.

Pregnancy and HIV

One of the success stories of HIV treatment is the dramatic reduction in perinatal transmission when babies are born to HIV-infected mothers. It is currently estimated that fewer than 250 infected children are born yearly in the United States.[37] The linchpin of the current strategy lies in the use of antiretroviral therapy both antepartum and intrapartum as well as infant postexposure prophylaxis and the avoidance of breast feeding. Women who wish to become pregnant should be on a stable ART regimen with maximal suppression of viral load. The risk of transmission is < 1% in women with undetectable HIV viral load on treatment.[38] Antenatal and intrapartum ART not only reduces HIV viral load in both the blood and genital secretions, but also results in systemic drug levels in the infant at the time of birth.[39] However, there is no known threshold of HIV RNA level at which there is no risk of transmission.[40]

Based on these observations, current recommendations are to begin ART in all pregnant women regardless of CD4 count and viral load, although delaying the initiation of therapy until after the first trimester can be considered.[12,39] Antenatal counseling should include a discussion about the known benefits of ART (reducing perinatal transmission and benefits to maternal health) as well as the risks, including the limited long-term outcome data for infants with in utero ART exposure. Certain ART regimens should be avoided, in particular those containing efavirenz, which is a potential teratogen (when given in the first trimester). (Interestingly, the latest WHO guidelines on prevention of MTCT recommend EFV during the second and third trimesters.) Toxicities and recommendations for the use of specific ARVs can be found in Table 3 of the recently updated Public Health Service Task Force guidelines for the reduction of perinatal HIV transmission.[39]

Post-Exposure Prophylaxis (PEP)

The risk of HIV transmission per act is generally low, but varies substantially by mode of transmission and other mitigating factors. The estimated risk of infection for the most common modes of transmission are:[12,41]

- Contaminated blood transfusion: 95 in 100;
- Perinatal transmission from mother to child: 1 in 4;
- Needle sharing: 1 in 150;
- Occupational needle stick: 1 in 300;
- Male to male receptive anal intercourse: between 1 in 10 to 1 in 1600;
- Male to female vaginal intercourse: between 1 in 200 to 1 in 2000;
- Female to male vaginal intercourse: between 1 in 700 and 1 in 3000.

Occupational Exposure

The risk of an occupational HIV transmission varies with the type and severity of exposure. Studies have shown that with exposure to HIV-infected blood, percutaneous needlestick injury carries an approximately 0.3% risk of transmission and a mucous membrane exposure 0.09% risk. There have also been cases of HIV transmission through non-intact skin exposure. Potentially infectious body fluids include blood, CSF, genital secretions, breast milk, amniotic, pleural, peritoneal, pericardial, and synovial fluid. Unless visibly contaminated by blood, fluids such as urine, feces, nasal secretions, sputum, vomit, tears, and sweat are not considered infectious.[42] The initial evaluation should include a medical history and current medications for the patient, determining the HIV/HBV/HCV status of both the source and patient, and the details of the exposure (e.g., timing, hollow- vs. solid-bore needle, type of body fluid, intact vs. non-intact skin). While an undetectable viral load in the source patient likely indicates a lower risk of infection, it does not eliminate the possibility of transmission.

In a case-control study of healthcare workers (HCW) with occupational needlestick exposure to HIV-infected blood, the risk factors for seroconversion were: deep injury, injury with a device visibly contaminated with patient blood, a procedure that involved needle access to an artery or vein, and a source patient who died of AIDS within two months. Each of these correlates with a higher inoculum of virus in the exposure, either due to volume of blood or as a proxy for the viral load in the source patient. The prompt use of zidovudine was associated with an 81% decrease in risk of acquiring HIV.[43]

The recommended PEP regimen for needlestick and mucous membrane exposures depends on both

Table 4: CDC Recommendations for HIV Postexposure Prophylaxis for Percutaneous Injuries

Infection status of source					
Exposure type	**HIV-Positive Class 1***	**HIV-Positive Class 2***	**Source of unknown HIV status†**	**Unknown source §**	**HIV-Negative**
Less severe¶	**Recommend basic 2-drug PEP**	**Recommend expanded ≥ 3-drug PEP**	**Generally, no PEP warranted; however, consider basic 2-drug PEP** for source with HIV risk factors††	**Generally, no PEP warranted; however, consider basic 2-drug PEP** in settings where exposure to HIV-infected persons is likely	**No PEP warranted**
More severe§§	**Recommend expanded 3-drug PEP**	**Recommend expanded ≥ 3-drug PEP**	**Generally, no PEP warranted; however, consider basic 2-drug PEP** for source with HIV risk factors††	**Generally, no PEP warranted; however, consider basic 2-drug PEP** in settings where exposure to HIV-infected persons is likely	**No PEP warranted**

*** HIV-Positive, Class 1 — asymptomatic HIV infection or known viral load (e.g., <1,500 RNA copies/mL). HIV-Positive, Class 2 — symptomatic HIV infection, AIDS, acute seroconversion, or known high viral load. If drug resistance is a concern, obtain expert consultation. Initiation of postexposure prophylaxis (PEP) should not be delayed pending expert consultation, and, because expert consultation alone cannot substitute for face-to-face counseling, resource should be available to provide immediate evaluation and follow-up care for all exposures.**

† Source of unknown HIV status (e.g., deceased source person with no samples available for HIV testing).

§ Unknown source (e.g., a needle from a sharps disposal container).

¶ Less severe (e.g., solid needle and superficial injury).

** The recommendation "consider PEP" indicates that PEP is optional; a decision to initiate PEP should be based on a discussion between the exposed person and the treating clinician regarding the risks vs. benefits of PEP.

†† If PEP is offered and taken and the source is later determined to be HIV-negative, PEP should be discontinued.

§§ More severe (e.g., large-bore hollow needle, deep puncture, visible blood on device, or needle used in patient's artery or vein).

Adapted from U.S. Public Health Service Guidelines[42].

the severity of exposure and the infection status of the source patient. (*See Table 4.*)[42] Therapy should be started as soon as possible, preferably within 72 hours, and continued for 28 days. The theoretically increased efficacy of a three-drug PEP regimen should be carefully weighed against the frequent side-effects and poor adherence, especially in the setting of a low-risk exposure. Consider prescribing antiemetics and antimotility agents to be taken on a PRN basis as a significant proportion of patients starting PEP (which contains zidovudine) will experience gastrointestinal side-effects including nausea and vomiting. Safety labs (CBC, chemistries, and liver and renal function tests) should be performed at baseline and 2 weeks after initiating PEP. If the HCW has not been vaccinated for hepatitis B and there is a suspicion that the source patient is infected, then the hepatitis B vaccine and immunoglobulin can be provided up to 7 days after the initial exposure. Whenever possible, the source patient should be tested for HIV, and hepatitis B and C infection; postexposure prophylaxis can be stopped if the source patient tests HIV-negative. The HCW should have HIV testing at baseline, 4-6 weeks, and should be offered testing at 12 weeks and 6 months after exposure, although with current HIV EIAs, seroconversion will occur within 4 weeks in greater than 95% of cases if HIV infection occurs.[42]

Non-Occupational Exposure

Individuals may also seek care after possible non-occupational HIV exposure, which generally occurs through sexual contact. The initial evaluation should include the determination of the HIV status of the patient and source, the timing and characteristics of the exposure

Table 5: CDC Recommendations for HIV Postexposure Prophylaxis for Mucous Membrane Exposures and Nonintact Skin* Exposures

Infection status of source					
Exposure type	**HIV-Positive Class 1†**	**HIV-Positive Class 2†**	**Source of unknown HIV status§**	**Unknown source¶**	**HIV-Negative**
Small volume**	**Consider basic 2-drug PEP††**	**Recommend basic 2-drug PEP**	**Generally, no PEP warranted§§**	**Generally, no PEP warranted**	**No PEP warranted**
Large volume¶¶	**Recommend basic 2-drug PEP**	**Recommend expanded ≥ 3-drug PEP**	**Generally, no PEP warranted; however, consider basic 2-drug PEP†† for source with HIV risk factors§§**	**Generally, no PEP warranted; however, consider basic 2-drug PEP†† in settings where exposure to HIV-infected persons is likely**	**No PEP warranted**

*** For skin exposures, follow-up is indicated only if there is evidence of compromised skin integrity (e.g., dermatitis, abrasion, or open wound).**

† HIV-Positive, Class 1 — asymptomatic HIV infection or known low viral load (e.g., <1,500 RNA copies/mL). HIV-Positive, Class 2 — symptomatic HIV infection, AIDS, acute seroconversion, or known high viral load. If drug resistance is a concern, obtain expert consultation. Initiation of postexposure prophylaxis (PEP) should not be delayed pending expert consultation, and, because expert consultation alone cannot substitute for face-to-face counseling, resources should be available to provide immediate evaluation and follow-up care for all exposures.

§ Source of unknown HIV status (e.g., deceased source person with no samples available for HIV testing).

¶ Unknown source (e.g., splash from inappropriately disposed blood).

** Small volume (i.e., a few drops).

†† The recommendation, "consider PEP," indicates that PEP is optional; a decision to initiate PEP should be based on a discussion between the exposed person and the treating clinician regarding the risks vs. benefits of PEP.

§§ If PEP is offered and taken and the source is later determined to be HIV-negative, PEP should be discontinued.

¶¶ Large volume (i.e., major blood splash).

Adapted from U.S. Public Health Service Guidelines[42].

(e.g., type of intercourse, condom use, presence of trauma).[44] Baseline HIV testing should be performed to determine whether the patient was infected prior to the exposure. When the HIV status of the source individual is unknown, ideally that individual should be tested. If the risk of HIV exposure is considered high, PEP should be initiated until testing of the source patient is complete. Both animal studies and observational studies show evidence supporting the use of postexposure prophylaxis in patients with non-occupational HIV exposure.[44] Patients who have had unprotected sexual contact, injection drug use, or other high-risk exposures should be considered for PEP if they seek treatment within 72 hours of exposure. Clinicians must evaluate the risks and benefits of antiretroviral therapy on a case-by-case basis.

For those receiving PEP, treatment should be started as soon as possible and continued for a 28-day course. The preferred regimen is a three-drug combination comprised of two NRTIs with a protease inhibitor.[44] There is no evidence that any specific ART regimen is superior to others. The commonly used NRTI combinations are Truvada (tenofovir and FTC) or Combivir (AZT and 3TC), and the recommended protease inhibitor is ritonavir-boosted lopinavir (Kaletra). Efavirenz can also be used, but is teratogenic during the first trimester of pregnancy and generally should be avoided in women of child-bearing potential. Ritonavir is a potent inhibitor of cytochrome P450 and has a number of drug interactions that must be taken into account when initiating Kaletra. There is no clear evidence, though, that a three-drug ART regimen is superior to a two-drug regimen, but extrapolation from treatment of HIV-infected patients suggests that it should be used in very high-risk situations. A two-drug regimen (commonly Truvada or Combivir) can be considered for individuals at lower risk of transmission and for whom adherence and toxicity are major concerns. Consider prescribing antiemetics and antimotility agents to be taken on a PRN basis as a significant proportion of patients starting PEP will experience gastrointestinal side-effects including nausea and

vomiting, especially if prescribed AZT-containing regimens. Testing and prophylactic treatment for other sexually transmitted diseases including gonorrhea, chlamydia, and hepatitis B (for those not vaccinated) should also be considered. All patients seeking care after a potential HIV exposure should undergo HIV testing at 4-6 weeks, 3 months, and 6 months after exposure.[44]

Emerging Topics

HIV and Aging. Antiretroviral therapy has dramatically increased the lifespan of those infected with HIV and caused a significant shift in the demographics. In 2005, 25% of all patients living with HIV/AIDS were older than age 50, but that figure is expected to rise to more than 50% by 2015.[45,46] In addition to the complications of ART as described above, HIV infection appears to accelerate the aging process, bringing on more rapid onset of frailty, bone loss, and age-related cognitive, metabolic, cardiovascular, kidney, and liver disease.[45,47] This likely occurs through the deleterious effects of chronic inflammation and immune activation.[48] Given these findings, the primary care physician will play an even more important role in keeping the older HIV patients healthy through the aggressive optimization of comorbid conditions and lifestyle counseling.

Vaccines. After several negative phase III HIV vaccine studies,[49,50] a recent study showed a significant protective effect of an HIV vaccine for the first time.[51] In this trial of more than 16,000 healthy Thai volunteers, the use of a recombinant canarypox vector vaccine with a recombinant gp120 subunit booster showed a 31% efficacy in preventing new HIV infections. While there was a modest benefit, this particular vaccine will not be developed further due to the relatively limited protective effect demonstrated and the cumbersome vaccine dosing schedule. As a result, it is likely that it will be at a minimum several years before an effective vaccine is ready for routine use to prevent infection.

Pre-Exposure Prophylaxis (PrEP). Community programs focused on behavioral change and HIV risk reduction have had a significant impact on the number of new infections, but rates of HIV transmission continue to be a challenge, especially among certain high-risk populations.[3] As an effective HIV vaccine appears to be many years away, the use of ART as pre-exposure prophylaxis is under study. Several randomized clinical trials are underway testing either tenofovir or tenofovir co-formulated with FTC (Truvada).[52] At this time, PrEP cannot be recommended for routine use as its efficacy, safety, and impact on drug resistance are still unknown.

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Physician CME Questions

1. In a low-risk patient with a positive EIA and Western blot, the approximate chance of a false-positive HIV test is:
   A. 1 in 250
   B. 1 in 2,500
   C. 1 in 25,000
   D. 1 in 250,000

2. Patients with suspected acute HIV infection should be provided HIV antibody testing (EIA and Western blot) along with testing for:
   A. HIV genotypic resistance
   B. HIV viral load
   C. HLA-B5701 genotype
   D. HIV phenotypic resistance

3. An HIV-infected patient has a CD4 count of 150. For which of the following conditions should he receive prophylaxis?
   A. *Pneumocystis jirovecii* pneumonia
   B. toxoplasmosis
   C. disseminated *Mycobacterium avium* complex infection
   D. histoplasmosis

4. Current antiretroviral therapy guidelines recommend that asymptomatic individuals start HIV treatment when the CD4 counts drops below:
   A. 50 cells/μl
   B. 200 cells/μl
   C. 400 cells/μl
   D. 500 cells/μl

5. Which of the following antiretroviral drugs should be avoided during pregnancy because of potential teratogenicity?
   A. abacavir
   B. tenofovir
   C. efavirenz
   D. Truvada

6. In a patient with CD4 count of 150, all of the following vaccines should be avoided *except*:
   A. hepatitis B
   B. intranasal influenza
   C. MMR
   D. varicella

7. By 2015, what percentage of the HIV-positive population is expected to be older than age 50?
   A. 10%
   B. 20%
   C. 30%
   D. more than 50%

CME Answer Key

1. D; 2. B; 3. A; 4. D; 5. C; 6. A; 7. D

Primary Care Reports

CME Objectives

Upon completion of this activity, participants should be able to:

- summarize recent, significant studies related to the practice of primary care medicine;
- evaluate the credibility of published data and recommendations related to primary care medicine;
- discuss the advantages and disadvantages of new diagnostic and therapeutic procedures in the primary care setting.

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Executive Editor: Russ Underwood

Specialty Editor: Shelly Morrow Mark

Director of Marketing: Schandale Kornegay

GST Registration No.: R128870672

Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

POSTMASTER: Send address changes to Emergency Medicine Reports, P.O. Box 740059, Atlanta, GA 30374.

Back issues: $26. Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

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The essential monthly primary care update

By Louis Kuritzky, MD

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Hospital Medicine Alert, Infectious Disease Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports.*

VOLUME 15, NUMBER 7 PAGES 13-14 JULY 2010

Coronary Calcium Scores enhance risk prediction

Source: Polonsky TS, et al. *JAMA* 2010; 303:1610-1616.

PROBABLY THE MOST WIDELY RECOGNIZED scoring system for predicting CV risk is the Framingham Risk Score (FRS). The United States Preventive Services Task Force (USPSTF) has recently published the opinion that novel risk markers such as C-reactive protein do not sufficiently enhance risk prediction enough to justify their routine utilization in addition to traditional scoring systems like FRS Coronary Calcium Score (CCS) has a number of appealing attributes that suggest consideration as a powerful prediction tool.

In the Multi-Ethnic Study of Atherosclerosis (MESA) trial of persons without known CHD at baseline, a CCS > 300 was associated with a 10-fold increased risk for CHD events. A critical issue, however, is whether new or additional prediction score tools add meaningfully to existing methods. A metric known as Net Reclassification Improvement (NRI) has been recently proposed to distinguish whether the incremental impact of a scoring system or risk factor upon already existing methods is meaningful.

Using the cohort of MESA (n = 6814 adults; age > 45), Polonsky et al compared risk prediction as derived from FRS vs FRS + CCS. The addition of CCS to FRS resulted in a statistically significant NRI. An additional 23% of persons who experienced CHD events but had not been identified by FRS as high risk were correctly reclassified by the addition of CCS. Similarly, an additional 13% of subjects not classified by FRS as low risk (and who did not suffer events), were reclassified as low risk by the addition of CCS. Whether the preferential (or additional) use of CCS for risk prediction can improve outcomes over traditional risk scores alone will require further definition, although many are already sufficiently encouraged by the predictive power of CCS to currently employ it. ■

Exacerbations of COPD: Not so innocent

Source: Donaldson GC, et al. *Chest* 2010;137:1091-1097.

ACUTE EXACERBATIONS OF COPD (AE-COPD) are sometimes misconstrued as minimally consequential "bumps in the road" along the journey of progressive COPD. Unfortunately, the toxicity of ae-COPD has been underappreciated; ae-COPD are associated with hospitalizations, loss of lung function that is typically not regained, and mortality. Donaldson et al direct our attention to a newly recognized additional burden of morbidity associated with ae-COPD: MI and stroke.

The Health Improvement Network (THIN) database contains anonymized medical records of patients seen by GPs in England and Wales. Over a 2-year period, 25,857 COPD patients provided a dataset with which to compare the incidence of MI and stroke during "stable" periods of COPD with the immediate post-ae-COPD period.

The incidence of acute MI was increased more than 2-fold in the 5-day period immediately following an ae-COPD; similarly, stroke incidence was increased more than 2-fold in the 49-day period immediately post-ae-COPD. Both findings were statistically significant.

No pharmacologic treatment of COPD has been proven to be disease-modifying. Yet, since various pharmacotherapies have been shown to reduce ae-COPD, perhaps such treatments will ultimately be shown to impact disease outcome by affecting the above-mentioned consequences of ae-COPD: increased stroke and MI. ■

Vitamin E, but not pioglitazone, improves NASH

Source: Sanyal AJ, et al. *N Engl J Med* 2010;352:1675-1685.

STEATOSIS IS THE ACCUMULATION OF FAT, derived primarily from triglycerides in hepatic cells. Progressive steatosis can lead to hepatic inflammation, which, when not associated with alcohol, is known as non-alcoholic steatohepatitis (NASH). Obesity and diabetes are the two conditions most commonly associated with NASH. Because as many as 15% of NASH cases may ultimately progress to cirrhosis, effective treatments are eagerly sought.

Since the pathologic underpinnings of NASH often include insulin resistance, hypetriglyceridemia, and type 2 diabetes, pharmacology with thiazolidinediones (TZD) appears logical. Unfortunately, results from pilot trials of TZDs have been conflicting.

The NASH Clinical Research Network, established by the NIDDK, conducted a

placebo-controlled trial of pioglitazone or vitamin E in non-diabetic NASH patients (n = 247). Subjects received 800 IU/d vitamin E, 30 mg/d pioglitazone, or placebo for approximately 2 years. The primary outcome was histologic status of NASH.

At 96 weeks, vitamin E did demonstrate a statistically significant rate of NASH histologic improvement, but pioglitazone did not. Even though there were some favorable histologic effects, neither intervention showed a reduction in hepatic fibrosis, so we remain uncertain about whether vitamin E can impact the development of serious long-term liver disease. Pioglitazone did not achieve an effect on the primary outcome, but explanations for why TZDs may still be considered for NASH therapy are presented by the authors. ■

Best use of home BP monitoring

Source: Pickering TG, et al. *J Am Soc HTN* 2010;4:56-61.

The largest body of information guiding treatment of hypertension (HTN) is based upon office BP management. Nonetheless, home BP monitoring (HBPM) is documented to be a better predictor of CV risk than office BP. For instance, patients with high office BP but low HBPM are recognized to be at substantially lower risk than office BP predicts; similarly, high HBPM pressures compared to office BP portends greater risk than indicated by office BP alone. Simply the fact that HBPM offers the opportunity for many more BP readings than is readily accessible in clinical care provides both a more comprehensive and consistent BP profile.

Recording HBPM twice daily (morning and evening), when averaged over 1 week, provides a sufficient BP profile to help guide management. By HBPM, HTN is > 135/85 mmHg and normotension is < 125/75 mmHg. Borderline HBPM (125-135/75-85 mmHg) merits consideration of 24-hour ambulatory BP monitoring for further clarification. The authors, writing on behalf of the American Society of Hypertension, provide a list of validated home BP monitoring devices at: www.dableeducational.org/. ■

Suicide risk with anticonvulsants

Source: Patorno E, et al. *JAMA* 2010;303:1401-1409.

Although the term "anticonvulsant" is indicative of a therapeutic class, pharmacologically the class is diverse. Despite dissimilarities, an analysis by the FDA (2008) discerned a relative doubling of suicide behavior/ideation in anticonvulsant recipients compared to placebo, resulting in a change in labeling.

The HealthCore Integrated Research Database provides data with which to assess the relative risk for suicidal acts in persons receiving a variety of anticonvulsant agents. During a 5-year interval (2001-2006), almost 300,000 new prescriptions for various anticonvulsants were documented in this population. When compared to treatment with either topiramate or carbamazepine (reference drugs), important distinctions emerged in reference to suicidal acts and violence. For instance, the hazard ratio for suicidal acts was 1.42 for gabapentin, 1.84 for lamotrigine, and 1.65 for valproate, compared to topiramate.

The mechanism by which some anticonvulsants incur an increased suicide risk is not known, despite the recognition that anticonvulsants can have impact upon mood. The first 2 weeks after initiation is recognized to be a higher risk period. Clinicians should be vigilant for behavior or mood changes in patients treated with anticonvulsants, noting lesser apparent risk for topiramate or carbamazepine. ■

For type 2 diabetes, after metformin, what next?

Source: Phung OJ, et al. *JAMA* 2010;303:1410-1418.

In the absence of contraindications, metformin is the preferred initial treatment for most patients with type 2 diabetes (DM2). Unfortunately, monotherapy is unlikely to maintain adequate glycemic control, requiring additional treatment. Although the addition of insulin to metformin is an appropriate next step, and has been labeled Tier 1 in the most recent guidelines published by the American Diabetes Association, some patients are reluctant to use insulin, and the considerable weight gain experienced by some insulin users, as well as risk of hypoglycemia, is problematic.

Among the non-insulin therapeutic choices, there is a great degree of variation in tolerability issues, such as amount of weight gain and frequency/severity of hypoglycemia that may help guide treatment decisions. Phung et al analyzed data from 27 randomized controlled trials (n = 11,198), most of which were 6 months or less in duration, to compare weight changes and hypoglycemia when non-insulin agents were added to metformin.

As might be anticipated, when TZDs, sulfonylureas, and glinides were added to metformin there was a 1.8-2.1 kg weight gain. GLP-1 mimetics, alpha-glucosidase inhibitors, and DPP-4 inhibitors were either weight neutral or associated with minimal weight loss. Sulfonylureas were associated with higher rates of hypoglycemia.

Of course, progressive treatment of DM2 must be individualized, and should include consideration of characteristic tolerability issues such as weight gain and hypoglycemia. ■

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In this issue: *New reports about proton pump inhibitors and the effects of gastric suppression, pioglitazone vs vitamin E for non-alcoholic steatohepatitis, metformin and vitamin B12 deficiency, and FDA Actions.*

PPIs, C. difficile, and bone fractures

Since H2 antagonists were introduced 30 years ago followed by proton pump inhibitors (PPIs) 20 years ago, there has been speculation whether long-term gastric acid suppression might have adverse effects. Billions of doses later, there is new evidence that chronic PPI use may lead to infections, especially *Clostridium difficile* infection (CDI), and may also contribute to bone fractures.

In the first of several studies published in the May 10 issue of *Archives of Internal Medicine*, researchers looked at more than 101,796 discharges from a tertiary care medical center during a five-year period, reviewing the level of acid suppression therapy and its relationship to CDI. As the level of acid suppression increased, the risk of CDI increased from 0.3% in patients not receiving acid suppressive therapy to 0.6% in those receiving H2 antagonists to 0.9% in those receiving daily PPIs and finally 1.4% in those receiving high-dose PPI therapy. After adjustment for a number of factors including comorbid conditions, age, and antibiotic use, the odds ratio for CDI infections were: 1 with no acid suppressing treatment, 1.53 (95% confidence interval [CI], 1.12-2.10) with H2 antagonist, 1.74 (95% CI, 1.39-2.13) with PPIs, and 2.36 (95% CI, 1.12-2.10) with high-dose PPI therapy. The authors conclude that increasing levels of pharmacologic acid suppression are associated with increased risk of nosocomial *C. difficile* infections, and the risk increases with more aggressive acid suppression (*Arch Intern Med* 2010;170: 784-790).

In a second study from the same journal, researchers from the VA system in Massachusetts performed a retrospective, cohort study of 1166 inpatients and outpatients with CDI to determine if PPI use affected recurrence rates. During treatment for CDI, 45% of patients received a PPI while 55% did not. Recurrent CDI was more common in those exposed to PPIs than in those not exposed (25.2% vs 18.2%). The hazard ratio for recurrent CDI in those exposed to PPIs was 1.42 (95% CI, 1.11-1.82). The risk was higher in patients older than 80 years and in patients exposed to antibiotics not targeted to CDI infections The authors conclude that PPI use during treatment for CDI was associated with a 42% increased risk of recurrence (*Arch Intern Med* 2010;170:772-778).

It has also been postulated that suppressing gastric acid may affect digestion and absorption of certain nutrients, specifically calcium. Although this has never been definitively proven, multiple studies have shown that chronic PPI use is associated with bone fractures. The most recent study, also published in the May 10 issue of *Archives of Internal Medicine*, was a prospective analysis of more than 160,000 women enrolled in the

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Women's Health Initiative study. In more than 1 million person-years of follow-up, there were 1500 hip fractures, 4881 forearm or wrist fractures, 2315 clinical spine fractures, and more than 21,000 total fractures. The multivariate-adjusted hazard ratios for current PPI use was 1 for hip fracture, 1.47 (95% CI, 1.18-1.82) for clinical spine fracture, 1.26 (95% CI, 1.05-1.51) for forearm or wrist fractures, and 1.25 (95% CI, 1.15-1.36) for total fractures. Bone mineral density did not vary between PPI users and non-users. The authors conclude that use of PPIs in women was not associated with hip fractures but was modestly associated with clinical spine, forearm or wrist, and total fractures (*Arch Intern Med* 2010;170:765-771). This study confirms the findings of several large epidemiological studies that suggest that PPI use is associated with increased osteoporotic fracture risk. On May 25, the FDA issued a warning regarding the possible fracture risk associated with high-dose long-term use of PPIs. The Agency will require labeling changes to describe the possible risk.

As noted in these studies, PPI use is associated with risk of osteoporotic fractures and *Clostridium difficile* infections. Other studies have linked the PPIs to a higher risk of hospital- and community-acquired pneumonia, as well as enteric infection such as *Salmonella* and *Campylobacter* gastroenteritis. In an editorial in the May 10 issue of *Archives of Internal Medicine*, Mitchell Katz, MD, notes that of the more than 110 million prescriptions for proton pump inhibitors filled each year, many are for inappropriate indications, making PPIs one of the most overprescribed medication classes in the world. He suggests that "for most patients the adverse effects of PPIs outweigh the benefits" and urges physicians to offer other treatments for dyspepsia, prescribe shorter courses, and consider a trial of discontinuing PPIs in patients who are asymptomatic (*Arch Intern Med* 2010;170:747-748). ■

Pioglitazone vs vitamin E for NASH

Non-alcoholic steatohepatitis (NASH) is a common liver disease that is difficult to treat and often progresses to cirrhosis. A new study compares the thiazolidinedione pioglitazone (30 mg daily) to vitamin E (800 IU daily) in a placebo-controlled trial for 96 weeks in 247 nondiabetic NASH patients. The primary outcomes were standardized scores for steatosis, lobar inflammation, hepatocellular ballooning, and fibrosis as determined by liver biopsy. Vitamin E therapy was associated with a significant improvement in non-alcoholic steatohepatitis (43% vs 19%; $P = 0.001$), but pioglitazone did not show statistical improvement (34% vs 19%; $P = 0.04$). Serum transaminases improved with both treatments, and both reduced hepatic steatosis and lobular inflammation, but neither improved fibrosis. Pioglitazone caused significant weight gain compared to vitamin E or placebo. The authors conclude that vitamin E was superior to placebo for the treatment of NASH in adults without diabetes (*N Engl J Med* 2010;362:1675-1685). ■

Metformin and vitamin B12 deficiency

Monitor your patients on metformin for vitamin B12 deficiency. This is the message of a recent study from the Netherlands. The study enrolled 390 patients with type 2 diabetes on insulin and initiated metformin 850 mg three times a day or placebo for an average of 4.3 years. Metformin treatment was associated with a mean decrease in vitamin B12 concentrations of 19% ($P < 0.001$) and an increase in homocysteine concentrations of 5% ($P = 0.091$). Longer-term treatment with metformin was associated with larger declines in vitamin B12 levels. The authors conclude that metformin likely causes malabsorption of vitamin B12 and recommends routine monitoring of vitamin B12 levels in patients who are treated with metformin (*BMJ* 2010;340:c2181). ■

FDA actions

The FDA has approved a new formulation of oxycodone (OxyContin®) that is designed to discourage chewing, crushing, or dissolving the drug. The FDA admits, however, that although the new formulation reduces the risk of snorting or injecting the drug, it can still be abused by simply ingesting larger doses than recommended. Vocal critics have called for oxycodone's withdrawal from the market due to an explosion in abuse of the drug nationwide and calls this new formulation "too little too late."

The FDA has recommended resuming use of Rotarix® rotavirus vaccine and to continue using RotaTeq® rotavirus vaccine. Rotarix was found to have elements of the porcine circovirus 1 (PCV1) in March, which resulted in an advisory to clinicians to stop using the vaccine. Subsequently, DNA from PCV1 and PCV2 was discovered in the RotaTeq vaccine. The FDA now says that there is no evidence that PCV causes illness or infection in humans while the benefits of the vaccine are substantial. ■