Volume **18** Issue **1** February/March **2010**

Topics in HIV Medicine®

A publication of the International AIDS Society–USA

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Topics in HIV Medicine (formerly *Improving the Management of HIV Disease*) is published by the International AIDS Society–USA. This journal is intended to be a resource for physicians and other health care practitioners who are actively involved in HIV and AIDS care.

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Topics in HIV Medicine is published 4 to 6 times a year. To obtain a complimentary subscription or notify the International AIDS Society–USA of a change in address, please contact the International AIDS Society–USA at the address listed below or use the Subscription Request/Address Change form at the back of this issue.

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Current and previous issues of *Topics in HIV Medicine* are available online at www.iasusa.org.

ISSN 1542-8826
Printed in USA on acid-free paper
March 2010

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The 12th Annual Clinical Conference for the Ryan White HIV/AIDS Program was supported by:

US Department of Health and Human Services, Health Resources and Services Administration, HIV/AIDS Bureau

Educational grants support the *Improving the Management of HIV Disease* national CME program. We gratefully acknowledge the following funders for 2010:

Substantial Grant Support

Merck & Co, Inc
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Generous Grant Support

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Additional funding for selected activities in the national program was provided by:

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Perspective

Pathogenesis of HIV Infection: Total CD4+ T-Cell Pool, Immune Activation, and Inflammation

Recent studies have yielded important findings on the pathogenesis of HIV infection. HIV infection leads to immune dysfunction through CD4+ T-cell depletion (immunodeficiency) and immune activation (immunosuppression). In vivo imaging studies of nonhuman primates indicate that the total body pool of CD4+ T cells may provide more accurate quantitation of immune depletion in HIV infection than the peripheral blood CD4+ count. Immune activation appears to be driven by both a homeostatic response to CD4+ cell depletion and an inflammatory response to HIV infection. The evidence is mounting that ongoing inflammation and coagulation account for the increased risk of serious nonopportunistic events in patients with HIV infection. Studies in long-term nonprogressors indicate that the HIV-specific immune responses in these patients are distinguished by clonal expansions of antigen-specific CD8+ T cells. Additional study of the precise mechanisms that allow immunologic control of infection in these patients may contribute to development of vaccines and immune-based therapies. This article summarizes a presentation made by H. Clifford Lane, MD, at the International AIDS Society–USA continuing medical education program held in May 2009 in Chicago. The original presentation is available as a Webcast at www.iasusa.org.

The pathogenesis of HIV infection includes depletion of the total body CD4+ T-cell pool, leading to immunodeficiency. This effect is accompanied by activation of numerous elements of the immune system, leading to a functional immunosuppression (ie, reduced function of remaining CD4+ cells) and a state of inflammation and coagulation that appears to underlie the increased risk of nonopportunistic complications observed in patients with HIV infection. Inadequate immune response to HIV infection allows ongoing viral replication, driving continued immune activation. Recent investigations have focused on clarifying the relationship between peripheral blood CD4+ T-cell count and the total body CD4+ T-cell pool, dissecting the role of immune activation and inflammation in the expanded spectrum of complications in HIV disease, and identifying potential correlates of protective immunity to HIV.

Dr Lane is the clinical director of the National Institute of Allergy and Infectious Diseases.

Characterization of Total CD4+ T-Cell Pool: In Vivo Imaging

The correlation between peripheral blood CD4+ counts and the spectrum of clinical manifestations of HIV disease, from generalized lymphadenopathy at higher counts to cytomegalovirus retinitis at low counts, is well defined and has been recognized for many years. More recently, an association has been shown between peripheral blood CD4+ count and risk of nonopportunistic morbidity and mortality. For example, the CASCADE (Concerted Action on Seroconversion to AIDS and Death in Europe) study in treatment-naive patients and the D:A:D (Data Collection on Adverse Events of Anti-HIV Drugs) study in treatment-naive and treatment-experienced patients showed progressive increases in risk of all-cause mortality and non–AIDS-related mortality with decreasing CD4+ counts.

Despite its value, the peripheral blood CD4+ count is recognized as an imperfect marker of HIV disease progression. Baseline CD4+ counts explain only up to 30% of the variability in the time to reach AIDS or death (Mellors et al, *JAMA*, 2007). In patients who have undergone splenectomy or have received marrow-suppressive therapies such as interferon-alpha (IFN-α), the CD4+ percentage is a better marker of immune competence than CD4+ count. Further, given that only a small percentage (estimated at 2%) of the total pool of CD4+ cells are present in the blood at any moment in time, even a small change in the distribution of cells between the lymphoid tissues and blood could result in a large change in the peripheral blood CD4+ count.

Studies have recently been undertaken in the nonhuman primate simian immunodeficiency virus (SIV) model of HIV infection to better understand the relationships between the peripheral CD4+ count and the total CD4+ cell count in health and during SIV infection. In part, this interest was spurred by repeated statements at scientific meetings that approximately 70% of CD4+ cells are located in the gut. This figure seemed high and was difficult to validate with published experimental data.

To study the total CD4+ cell pool in nonhuman primates, a series of imaging studies were performed. A nondepleting humanized monoclonal antibody that binds to CD4 molecules from humans and rhesus macaques (CDR-OKT4A/hlgG4 [OKT4A]) was conjugated with indium 111 (^{111}In) in a manner similar to that used by Rubin and colleagues in 1996 to study CD4+ T-cell distribution in mice (*Proc Natl Acad Sci USA*, 1996). Semiquantitative in vivo images of CD4+ cell distribution were obtained using a single-photon emission computed tomography (SPECT) camera with normalization against liver uptake. Quantitative assessment of in vivo tissue binding by the labeled antibody was performed by ex vivo analysis of tissue in a gamma counter.

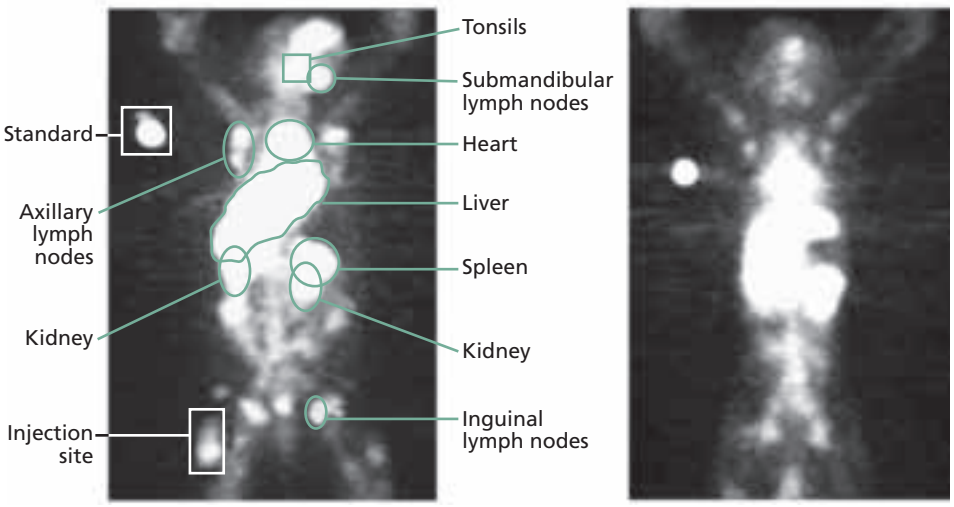

Figure 1. Total body imaging of CD4+ T-cell pool in 2 uninfected macaques, using indium 111–labelled anti-CD4 antibody. CD4+ counts: left, 1700 cells/μL; right, 1378 cells/μL. Adapted from Di Mascio et al, *Blood*, 2009.

Radioactivity was normalized against activity in the liver.

Macaques injected with ^{111}In-labeled antibody showed binding of the anti-CD4 antibody to CD4+ cells in vivo. A 10- to 20-fold increase in antibody binding was observed for CD4+ cells compared with CD4- cells derived from spleen, axillary lymph nodes, and mesenteric lymph nodes. Total body imaging of the CD4+ cell pool in uninfected monkeys with normal CD4+ counts showed that uptake of the antibody was highest in the lymph nodes, tonsils, spleen, blood pool of the heart, and liver (Figure 1). Studies of animals with SIV or simian-human immunodeficiency virus (SHIV) infection showed that the intensity of anti-CD4 antibody staining in lymphoid tissues (spleen, tonsils, lymph nodes) but not in non-lymphoid tissue (heart, kidney, marrow, testes) was proportional to the peripheral blood CD4+ count (Figure 2, A). Plots of the peripheral blood CD4+ counts versus radiotracer retention in lymphoid tissue showed an exponential relationship (Figure 2, C).

Thus, decreases in peripheral CD4+ count at relatively low counts are correlated with larger decreases in the total CD4+ cell pool than similar absolute decreases at higher CD4+ counts. The reduction in the total CD4+ pool is quite large as the peripheral cell count decreases below 200 cells/μL, an observation that fits well with the dramatic increase in risk of opportunistic conditions as peripheral cell counts decline and continue to fall below this value.

Of note, the density of CD4+ T cells in intestinal tissue appeared to be low. The gastrointestinal tract appeared to account for no more of the CD4+ pool than the spleen.

Immune Activation

T-cell activation can be measured in several ways. Proliferation can be assessed using an antibody to measure incorporation of bromodeoxyuridine (BrdU) into the DNA of cells during cell division (S phase of the cell cycle) and by measuring the reduction of intensity of staining with fluorescent carboxyfluorescein diacetate succinimidyl ester (CFSE), a dye that stains cell cytoskeleton and thus decreases by 50% with each cell division. Nonproliferation-based assessments of activation include measuring expression of cell surface markers such as HLA-DR, CD38, and programmed death-1 (PD-1) or measurements of intracellular proteins such as Ki67 and IFN-gamma (IFN-γ).

Immune activation in HIV infection includes 2 components: (1) the homeostatic response to CD4+ cell depletion, a compensatory mechanism that may include production of interleukin-7 (IL-7); and (2) an inflammatory response that includes both an HIV-specific immune response and "bystander" immune activation as a result of the HIV-specific immune response. In HIV infection, CD4+ cell activation and CD8+ cell activation are regulated differently, reflecting the different influences of these 2 forces on CD4+ and CD8+ T cells.

In a study in which T-cell proliferation was measured by BrdU incorporation, HIV-infected patients were categorized into 4 groups according to viral load and CD4+ count. The level of CD8+ cell activation was correlated almost exclusively with viral load (Figure 3). In contrast, the level of CD4+ cell activation was associated with both viral load and CD4+ cell depletion. The highest levels of CD4+ and CD8+ activation were in the subset of patients with high viral loads and low CD4+ counts. The second highest level of CD4+ activation occurred in patients with low CD4+ counts and low viral loads, whereas the second highest levels of CD8+ activation were in patients with high viral loads and high CD4+ counts.

The differences in activation of CD4+ and CD8+ cells are also evident from a study in patients with well-controlled viral loads (plasma HIV RNA levels < 50 copies/mL). As can be seen from Figure 3 (bottom), the level of CD4+ cell activation (BrdU incorporation) in HIV-infected individuals decreases as the CD4+ count increases and eventually becomes indistinguishable from that of HIV-uninfected subjects (Catalfamo et al, *Proc Natl Acad Sci USA*, 2008). Conversely, CD8+ cell activation in the HIV-infected group was always greater than that in the uninfected group. This persistent increase in CD8+ cell activation likely represents ongoing viral replication, even in patients with plasma HIV RNA levels below 50 copies/mL.

Inflammation as a Component of HIV Immune Activation

Patients with HIV infection are at increased risk of morbidity and mortality from a variety of nonopportunistic serious conditions, and it has become

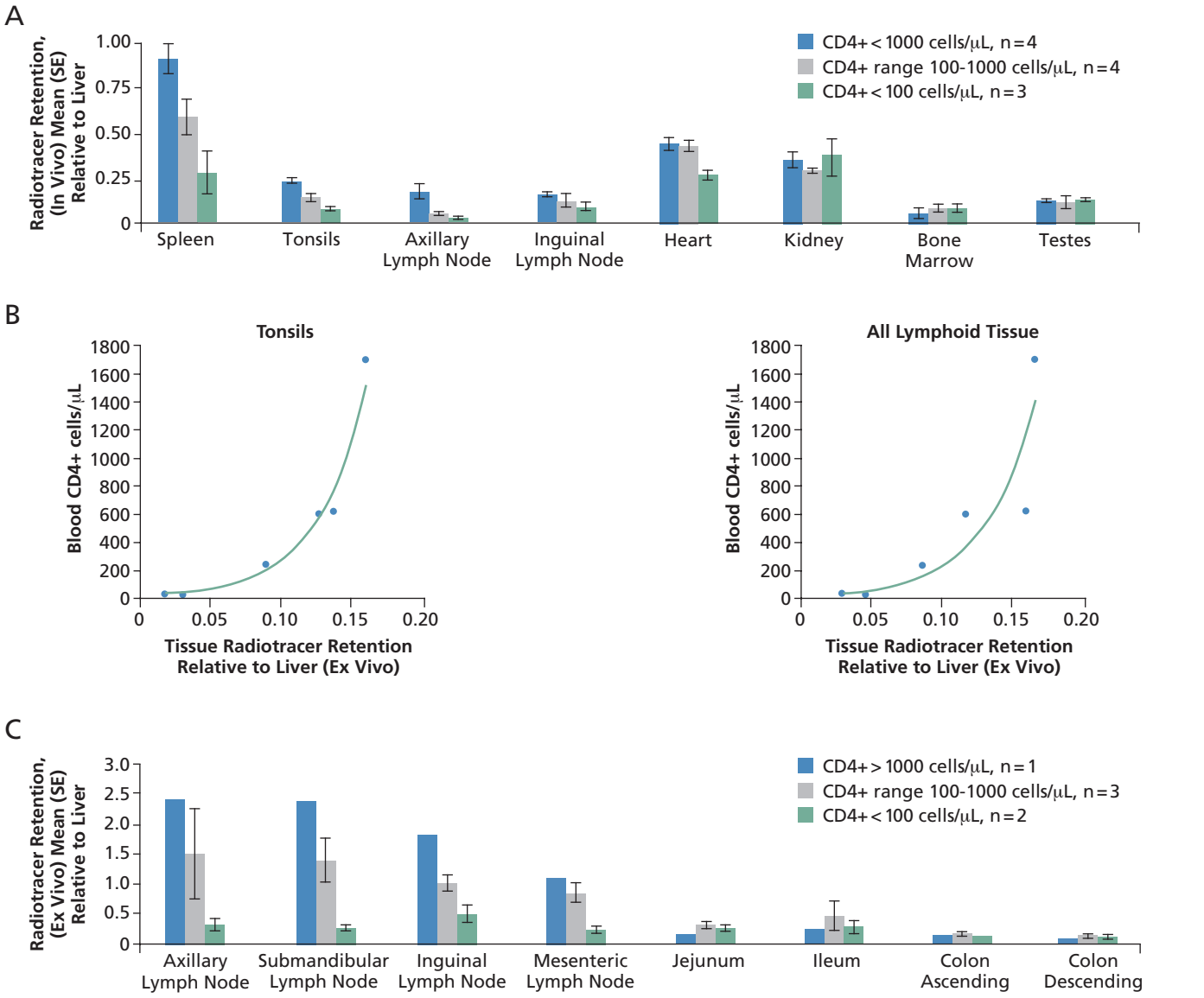

Figure **2**. Data from simian immunodeficiency virus– or simian-human immunodeficiency virus–infected and uninfected macaques, showing that intensity of in vivo staining of CD4+ cells in lymphoid tissues (A) was exponentially proportional to peripheral blood CD4+ counts (B). SE indicates standard error. Data from ex vivo tissue studies (C) showing density of CD4+ cells in lymphoid tissue and intestinal tissue according to peripheral blood CD4+ count. Adapted from Di Mascio et al, *Blood*, 2009.

increasingly clear that inflammation contributes to this increased risk. The SMART (Strategies for Management of Antiretroviral Therapy) trial compared strategies of drug conservation (intermittent antiretroviral therapy to maintain CD4+ counts above 250 cells/μL) versus continuous viral suppression with antiretroviral therapy. The goal of this trial was to determine whether reducing overall antiretroviral drug exposure might reduce the risk of non–AIDS-related complications potentially due to antiretroviral drugs such as heart disease, stroke, and liver failure. The study was stopped prematurely when it was found that patients in the drug-conservation group had a higher risk of non–AIDS-related events than did those in the continuous-treatment group, with a hazard ratio of 1.7 for all serious non–AIDS-related events.

These findings suggested that the increased risk of non–AIDS-related events was associated more with HIV replication than with drug toxicity. A subsequent analysis of biomarkers from stored samples showed that the risk of all-cause mortality was statistically significantly greater among patients with higher baseline levels of high-sensitivity C-reactive protein (adjusted odds ratio [OR], 2.8; $P = .03$); interleukin-6 (IL-6) (adjusted OR, 11.8; $P < .0001$); or the coagulation marker D-dimer (adjusted OR, 26.5; $P < .0001$) (Kuller et al, *PLoS Medicine*, 2008). In patients receiving intermittent antiretroviral therapy, increases in D-dimer

levels were statistically significantly associated with the increases in viral load at 1 month after stopping therapy.

These findings indicate that ongoing inflammation and a procoagulant state may underlie the increased risk of non–AIDS-related events observed in patients with HIV infection. The elevation of D-dimer levels may be particularly noteworthy because it suggests that ongoing coagulation in the context of ongoing inflammation may lead to small-vessel damage and ultimately to end-organ damage.

Host Control of HIV Infection

Understanding how some patients are able to spontaneously control HIV infection remains one of the great challenges in HIV science. In most infected individuals, HIV replication continues despite a high frequency (10% – 40%) of very broad (15 – 20 epitopes) CD8+ cell responses to autologous virus. That is, the CD8+ cells respond to viral antigens, but the response is inadequate to control infection. The exceptions are a group of patients who maintain plasma HIV RNA levels below 50 copies/mL and normal CD4+ counts in the absence of antiretroviral therapy. Even in these patients, however, there is evidence of the presence of virus, with proviral DNA and antibody to HIV found in all and HIV RNA detected in most. This long-term nonprogressor phenotype is highly associated with certain HLA genotypes, particularly the HLA-B*5701 genotype. Achieving an understanding of the precise immunologic mechanisms leading to this control is of great importance to the development of vaccines and immune-based therapies.

A recent study assessed CD8+ cell profiles in long-term nonprogressors, patients with viremic progression, and patients with HIV RNA levels of less than 50 copies/mL who were receiving antiretroviral therapy (Migueles et al, *Immunity*, 2008; Migueles et al, *Nat Immunol*, 2002). Long-term nonprogressors did not differ from viremic progressors in the percentage of their CD8+ cells responding to viral antigen by producing IFN-γ (Figure 4). However,

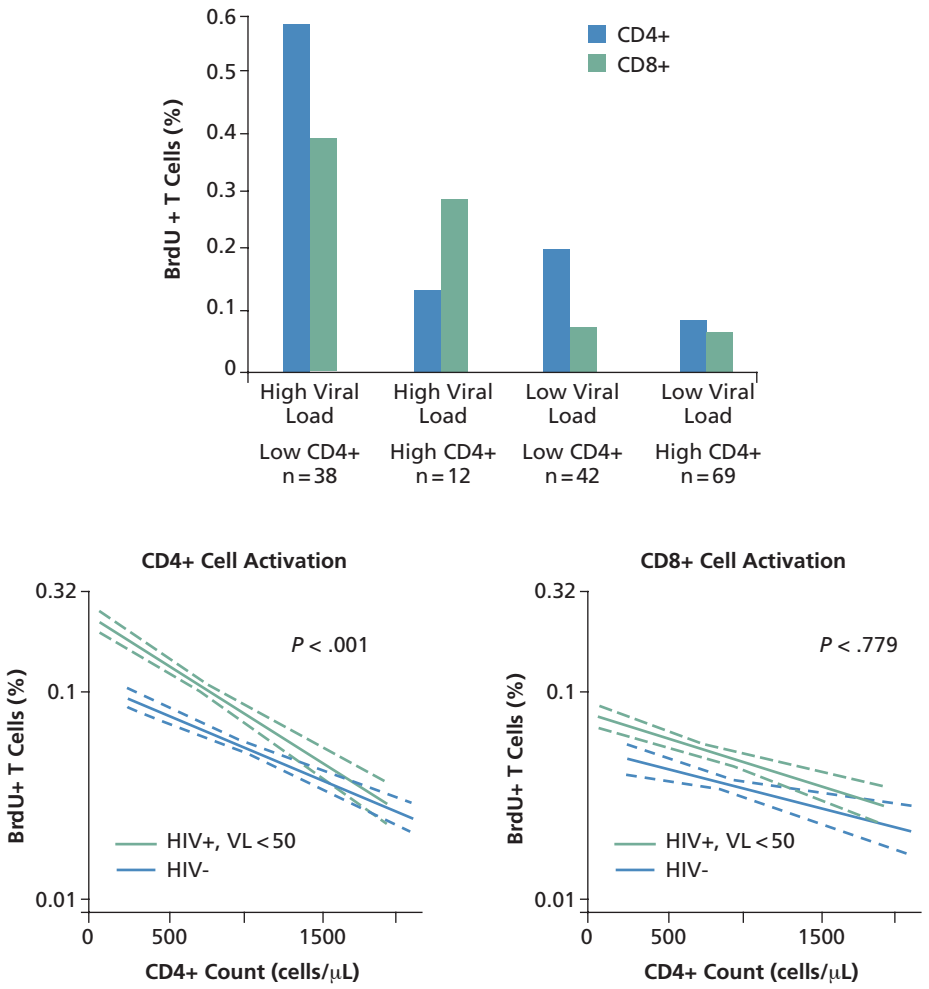

Figure **3**. Top, CD4+ and CD8+ cell activation (as measured by bromodeoxyuridine [BrdU] incorporation) according to viral load and CD4+ count in HIV-infected patients. Bottom, CD4+ and CD8+ cell activation according to CD4+ count in HIV-infected (HIV+) patients with plasma HIV RNA level (VL) < 50 copies/mL and in uninfected (HIV-) subjects. Dashed lines indicate 95% confidence intervals; *P* values reflect the differences between the slopes of the 2 lines in each graph. Adapted from Catalfamo et al, *Proc Natl Acad Sci USA,* 2008.

proliferation of CD8+ cells, measured by CFSE staining, was statistically significantly greater in long-term nonprogressors than in either viremic progressors or patients with viral suppression who were receiving antiretroviral therapy. This finding suggests that a distinguishing immunologic feature in the long-term nonprogressors is the clonal expansion of activated cells in response to antigen. The cells undergoing clonal expansion have also been found to express perforin and granzyme B, key components of the cellular machinery activated during cell-mediated killing.

At the National Institutes of Health (NIH), a study is being conducted to determine whether or not transfer of cells from a long-term nonprogressor to an HLA-matched progressor can confer protective immunity to HIV. The study plan involves obtaining peripheral blood mononuclear cells from an HLA-B*5701-positive long-term nonprogressor donor (plasma HIV RNA level < 50 copies/mL; CD4+ count ≥ 400 cells/μL; no antiretroviral drugs for ≥ 1 year) and infusing those cells to an HLA-B*5701-positive patient with failure of at least 2 antiretroviral regimens, HIV RNA level above 10,000 copies/mL, and CD4+ count below 200 cells/μL. Readers are encouraged to e-mail the researchers at the NIH (caldararo@niaid.nih.gov)

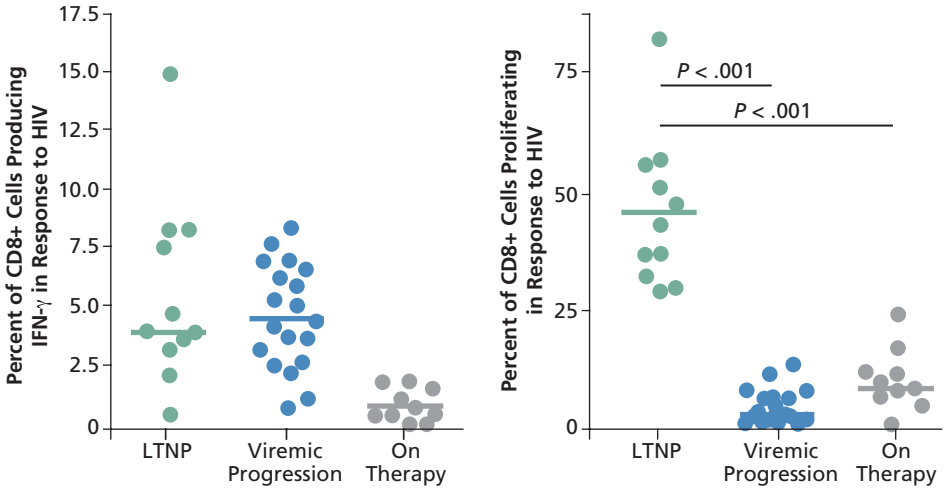

Figure **4**. Percent of interferon-gamma (IFN-γ)-producing CD8+ cells and proliferation of CD8+ cells (measured by carboxyfluorescein diacetate succinimidyl ester staining) in long-term nonprogressors (LTNP), viremic patients with progression, and patients with plasma HIV RNA level < 50 copies/mL who were receiving antiretroviral therapy. Left graph adapted from Migueles et al, *Immunity*, 2008; right graph adapted from Migueles et al, *Nat Immunol*, 2002.

should they know of a patient with potential interest in this study.

Summary

Recent investigations into the pathogenesis of HIV infection have yielded important insights. HIV infection leads to a depletion of the CD4+ T-cell pool that may be quantitated by in vivo imaging. There appears to be an exponential relationship between the peripheral blood CD4+ T-cell count and the total body CD4+ T-cell pool. The immune activation caused by HIV infection is driven by viral load and homeostatic forces and produces a state of chronic inflammation and coagulation that may lead to substantial end-organ damage outside of the immune system. A small subset of patients with HIV infection exhibit control of viral replication in the absence of treatment. This control appears to be mediated via a unique CD8+ cell response that identifies an important target for potential HIV vaccines and HIV-specific, immune-based therapies.

Presented by Dr Lane in May 2009. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Lane in December 2009.

Financial Disclosure: Dr Lane received research support from Novartis Pharmaceuticals Corp.

Suggested Reading

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Top HIV Med. 2010;18(1):2-6
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Help Rebuild GHESKIO

Every year, the International AIDS Society–USA partners with an HIV/AIDS charitable organization in a developing nation severely impacted by HIV.

This year, the IAS–USA is turning its attention to assisting in rebuilding GHESKIO, Haiti's largest provider of HIV/AIDS care, treatment, education, and research. For more than 20 years, GHESKIO has served as the Haitian government's research and training center for HIV/AIDS. It is now an internationally recognized center of excellence, under the leadership of Dr Jean William Pape.

In the Heart of Port-Au-Prince: GHESKIO in Haiti

GHESKIO Center in Port-au-Prince is a non-governmental organization that has provided continuous medical care in Haiti since 1982—never once shutting its doors or charging fees.

Since the January 12th, 2010, earthquake GHESKIO has been providing humanitarian assistance and emergency care to those affected by the disaster and continues to provide life-saving medications to people with HIV/AIDS.

How You Can Make a Difference

GHESKIO will be rebuilt, one brick at a time. You can help provide refugee relief and urgent medical care by donating funds to support GHESKIO medical clinic in Haiti. Weill Cornell Medical College (WCMC) has been collaborating with GHESKIO for 25 years in research, care and prevention of HIV/AIDS. Both WCMC and IAS–USA are 501(c)(3) organizations, and your donation is tax deductible. Both organizations are donating their administrative costs to ensure that 100% of every dollar donated goes directly to GHESKIO.

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Perspective

Medical Interventions for Addictions in the Primary Care Setting

Primary care physicians treating HIV-infected patients should not be afraid or reluctant to engage in medication-assisted treatment for substance dependence. Effective medications are available for many types of substance addictions, including buprenorphine for opioid dependence, disulfiram for cocaine dependence, bupropion for methamphetamine dependence, and naltrexone for alcohol dependence. Physician use of medications coupled with encouragement to adhere to all aspects of treatment including counseling and other psychosocial interventions can produce substantial rewards in terms of keeping patients involved in their HIV care and improving overall patient health and functioning. This article summarizes a presentation made by R. Douglas Bruce, MD, MA, MSc, at the 12th Annual Clinical Conference for the Ryan White HIV/AIDS Program held in October 2009 in Dallas, Texas. The original presentation is available as a Webcast at www.iasusa.org.

The National Institutes of Health consensus on drug treatment for substance dependence emphasizes that drug addiction is a disorder of the brain and therefore a medical disorder. It calls for broader access to drug treatment and reduced federal and state barriers to treatment, and it stresses the importance of providing substance dependence counseling, psychosocial therapies, and other supportive services.

Just as pharmacologic therapy can improve depression, medications can assist in the successful treatment of opioid, cocaine, methamphetamine, alcohol, and nicotine dependence, and can thereby improve practitioners' abilities to keep these patients connected to their HIV care. Primary care practitioners should not be reluctant to engage in drug treatment for substance dependence in their HIV patients.

The Problem: Addiction

Drug addiction has many and well-known adverse consequences for the individual and for society. Despite these negative consequences, people continue to engage in drug use for a variety of reasons. Some people take illicit drugs to *feel good*—that is, to have novel feelings, sensations, and experiences and to share them—whereas others take them to *feel better*—that is, to lessen the symptoms of anxiety, fears, depression, and hopelessness. Indeed, the prevalence of major depressive disorder is more than 50% among opioid-dependent patients in some data sets.

Addiction is a state in which a person engages in a compulsive behavior that is reinforcing—pleasurable or rewarding—and there is loss of control in limiting the intake of that addictive substance. Understanding why some people become addicted to substances and others do not will help clarify strategies for prevention and treatment. Vulnerability to addiction is on a spectrum between genetics (biology) and environmental factors. Specifically, some individuals are genetically predisposed to specific addictions so even a brief exposure to a substance will produce very reinforcing effects. In contrast, some individuals may not be genetically predisposed to find a particular substance as reinforcing as the addictive group; however, these individuals may reside in environments that promote or make easily available particular substances.

As for the biology underlying addiction, the answers to most questions on this topic revolve around dopamine and dopamine receptors. An early study by Volkow and colleagues (*Am J Psychiatry,* 1999) in nonaddicted subjects indicated that those with

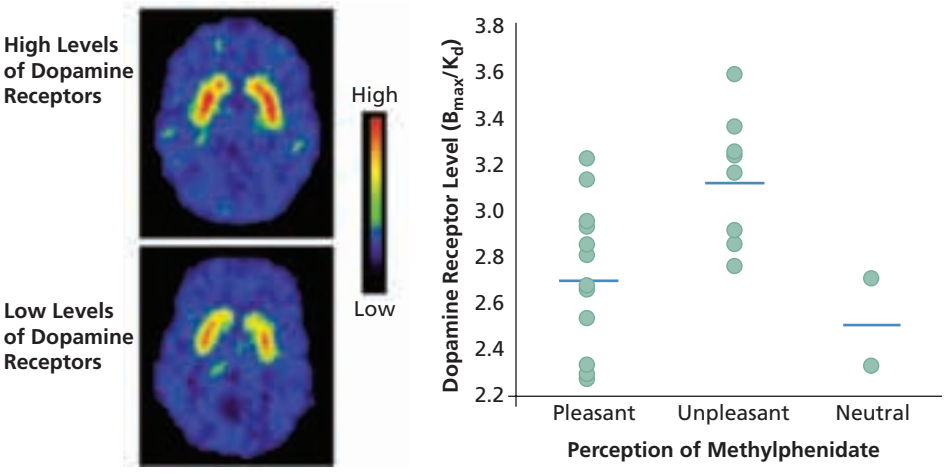

Figure **1**. Perception of methylphenidate use according to dopamine receptor levels in nonaddicted subjects. B_{max} indicates receptor density; K_d, receptor affinity; horizontal lines, means for the different groups. Adapted from Volkow et al, *Am J Psychiatry*, 1999. Photos reprinted with permission from *Am J Psychiatry* (copyright 1999). American Psychiatric Association.

Dr Bruce is assistant professor of medicine at Yale University School of Medicine in New Haven, Connecticut.

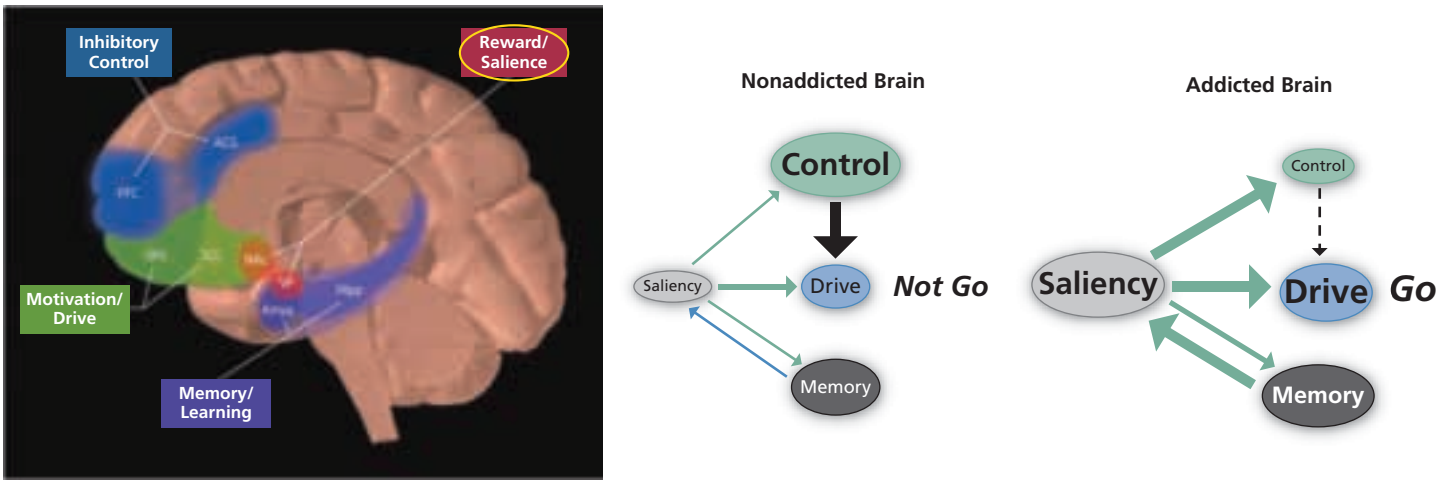

Figure **2**. Brain circuits involved in drug use and addiction (left). ACG indicates anterior cingulate gyrus; Amyg, amygdala; Hipp, hippocampus; NAc, nucleus accumbens; OFC, orbitofrontal cortex; PFC, prefrontal cortex; SCC, subcallosal cortex; VP, ventral pallidum. Adapted from National Institute on Drug Abuse Web site, 2010. Schematic of changes in brain circuits with addiction (right). Adapted from Volkow et al, *Neuropharmacology*, 2004.

lower concentrations of dopamine receptors in the brain find the stimulant methylphenidate "pleasant," whereas those with higher dopamine receptor levels find it "unpleasant" (Figure 1). Numerous brain circuits, however, are involved in drug use and addiction, representing the mechanisms of reward and salience, as well as those of memory and learning, motivation and drive, and inhibitory control (Figure 2). All of these must be considered in strategies to treat addiction effectively.

Studies of dopamine release in the nucleus accumbens of rats, one of the brain centers involved in reward and salience, showed that the natural rewards of food and sex are associated with peak increases in dopamine level of approximately 150% and 200%, respectively (Bassareo and Di Chiara, *Neuroscience*, 1999; Fiorino et al, *J Neurosci*, 1997). In contrast, peak dopamine increases were 1000% above basal levels with amphetamine, 300% above with cocaine, 200% above with nicotine, and from about 150% to 200% above at different morphine doses (Di Chiara and Imperato, *Proc Natl Acad Sci USA*, 1988). Such results help explain the common finding that substance-dependent patients will engage in sexual risk behaviors for drugs or for money to obtain drugs because the end goal is more rewarding neurobiologically. In other words, if sex were the greater reward, the patient would stop further activity after sex; however, they experience far greater reward with the drugs than they do with the natural behaviors of food and sex.

Complicating this picture is the realization that numerous data indicate that dopamine 2 receptor levels are lower in addicted brains than in nonaddicted brains, and that addiction itself changes brain circuits involved in saliency, drive, control, and memory (Figure 2). This emphasizes the challenge of treating the substance user: if medical practitioners are unable to have patients be sexually abstinent (because sex is less rewarding than heroin use) by counseling the patient on the risks of a sexually transmitted disease, for example, they must look beyond simple advice and consider prescribing medications that may assist the patient in achieving sobriety. Thus, illicit drugs usurp naturally occurring brain circuits and alter associated motivational priorities, and thereby change behavior. This is why substance-dependent patients cannot "just quit" and why comprehensive treatment, including the prescription of medications to assist in achieving sobriety, are essential.

Pharmacology in Primary Care

Treatment for addiction includes pharmacologic treatment, behavioral therapies, medical treatment for complications of addiction (eg, HIV and hepatitis C virus [HCV] infection), and social services. The author came to the field of treating addiction from working in the HIV disease treatment field. In some sense, treating addiction with drug therapy is simpler than managing HIV infection with drug therapy, in that resistance does not develop to treatments for addiction. If a practitioner can manage the pharmacotherapy of HIV infection, that medical practitioner is already well equipped to incorporate medication-assisted treatment strategies to help manage treatment of addiction. The following sections provide an overview of medication treatment strategies for various addictions.

Buprenorphine for Opioid Dependence

Heroin is a short-acting, semisynthetic opioid produced from opium. The rationale for treating heroin dependence with buprenorphine is to satisfy the brain's craving for an opioid in a safe and controlled manner. In contrast to heroin, the use of which is character-

ized by rapidly alternating states of craving and satiety, buprenorphine, for example, permits a steady release of dopamine, bringing some stability to the patient's neurobiology and some organization to what is essentially a chaotic neurocognitive environment. This, in turn, allows practitioners and patients to concentrate on the business of deriving and maximizing benefits of HIV disease treatment, rather than spending time and resources dealing with drug-seeking behaviors, withdrawal, and other narcotics issues. Thus, the aim of providing opioid treatment is to provide cross-tolerance, preventing withdrawal and relieving the craving for opioids. In addition, buprenorphine provides a narcotic blockade that blocks the euphoric effect of exogenous opioids. In the primary care setting, buprenorphine remains the best option for the treatment of opioid dependence, as it has been shown to be superior to naltrexone (Schottenfeld et al, *Lancet*, 2008).

Buprenorphine is a partial opioid receptor agonist. Unlike full agonists (heroin, levo-alpha-acetylmethadol [LAAM], methadone, and morphine), which increase receptor-specific effects to a maximal effect with increasing dose, dose increases of buprenorphine result in a lesser increase in effects and a lesser maximal effect. Buprenorphine affects mu-opioid receptor availability by occupying available receptors in the brain, thereby satisfying the craving for an opioid and preventing any additional "reward" to be experienced from heroin use. Data reported in 2000 indicate that the percentage of patients retained in treatment over 17 weeks was 58% with buprenorphine, compared with 73% with high-dose methadone, 53% with LAAM, and 20% with low-dose methadone, respectively. Mean percentages of patients with opioid-negative urine were 40%, 39%, 49%, and 19%, respectively (Johnson et al, *N Engl J Med*, 2000).

Buprenorphine is a valuable tool, and the author believes every physician treating HIV-infected drug users should obtain a buprenorphine waiver and a special X number from the Drug Enforcement Agency so as to be ready to prescribe it (see buprenorphine.samhsa.gov for details on how to obtain licensure). Buprenorphine treatment is less complicated than the treatment of HIV or HCV infection. It is safer and less liable to abuse than is oxycodone as a treatment for pain or alprazolam as a treatment for anxiety. Also, its use can markedly expand patient involvement in their HIV treatment.

Disulfiram for Cocaine Dependence

Disulfiram, approved by the Food and Drug Administration (FDA) for the treatment of alcohol dependence, is also effective in treating cocaine dependence, a fact that does not seem to be widely appreciated. After an effect of decreasing cocaine use was observed in patients with joint alcohol-cocaine dependence, disulfiram was found to reduce cocaine use in cocaine-dependent patients receiving methadone. Six randomized controlled trials have now shown the efficacy of disulfiram in treating cocaine dependence (George et al, *Biol Psychiatry*, 2000; Carroll et al, Arch Gen Psychiatry, 2004; Petrakis et al, *Addiction*, 2000).

Disulfiram acts by inhibiting dopamine beta-hydroxylase activity, thus increasing dopamine levels in the brain (via a mechanism somewhat similar to that of cocaine). Compared with cocaine, which has a rapid onset of action and rapid attenuation of effect, leaving the dependent person constantly chasing the next "high," disulfiram is slow-acting. Again, the goal of treatment is to relieve the craving for dopamine by maintaining stable, elevated levels. Taking cocaine in addition to disulfiram frequently results in a nonrewarding, dysphoric response caused by excessive amounts of dopamine.

Although the dose of disulfiram that has been studied most extensively is 250 mg/d, practitioners in the author's clinic for HIV and HCV coinfected patients typically start treatment at around 125 mg/d because of the lack of data in this patient group and the concern about potential effects of disulfiram on aspartate aminotransferase and alanine aminotransferase levels. One problem with disulfiram treatment, as with other dependency treatments, is adherence. Treatment works well for motivated patients and for patients receiving disulfiram along with methadone maintenance. Disulfiram is underutilized in methadone programs and substance dependence programs. Primary care physicians can help increase the beneficial use of this valuable resource in their cocaine-dependent patients.

Bupropion for Methamphetamine Dependence

Methamphetamine can have profound effects on the central nervous system and can cause permanent brain damage. Methamphetamine users show a loss of dopamine transporters in the brain, and this loss is associated with slowing of motor reactions and memory loss (Volkow et al, *Am J Psychiatry*, 2001). The neurocognitive effects associated with methamphetamine use are exacerbated in HIV-infected patients, and reduced neurocognitive performance in these patients can severely compromise HIV disease care. The use of bupropion 150 mg twice daily produces some reduction in methamphetamine use among *mild* users of methamphetamine, with the mainstay of treatment being counseling. As with disulfiram for cocaine dependence, bupropion is not a panacea for methamphetamine use. Treatment may tip the balance for some patients in favor of greater stability of behaviors and better participation in HIV disease care.

Naltrexone for Alcohol Dependence

Naltrexone, an opioid receptor antagonist, is the most studied and consistently most effective pharmacotherapy for alcohol dependence (Anton et al, *JAMA*, 2006). Opioid receptor antagonists bind to but do not activate the receptor, and they prevent activation by full (eg, heroin, LAAM, methadone, and morphine) and partial (eg, buprenorphine) agonists. Alcohol stimulates receptor-mediated dopamine release through a complex mechanism

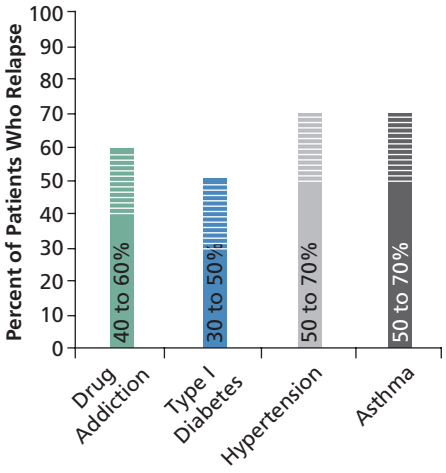

Figure **3**. Relapse rates for drug addiction compared with other common chronic illnesses. Adapted from McLellan et al, *JAMA*, 2000.

involving gamma-aminobutyric acid activation and the opioid receptor. By blocking the mu-opioid receptor, naltrexone acts to decrease the dopamine reward. Patients consume less alcohol while receiving naltrexone, and those who are sober while receiving treatment tend to have relapses of reduced severity. The currently recommended dosage is 100 mg/d, and vigilance for hepatotoxicity must be maintained (as indicated by the drug's black box warning). Expert opinion suggests that even lower doses of naltrexone may be effective in the treatment of alcohol dependence; therefore, medical practitioners should be encouraged that even low doses of the medication may be helpful in assisting patients to have improved health outcomes. Acamprosate and disulfiram are also FDA approved for treatment of alcohol dependence, but each is inferior to naltrexone.

The anticonvulsant drug topiramate, which appears to act at gamma-aminobutyric acid receptors, has been shown to be effective for alcohol dependence in several studies (Kenna et al, *Curr Drug Abuse Rev*, 2009; Johnson et al, *Arch Intern Med*, 2008) but is not FDA approved for the treatment of alcohol dependence. Doses vary by study, but generally treatment is started at low doses (eg, 25 mg/d) with titration to a maximum dose of 300 mg/d over 6 weeks. Topiramate has proved useful in decreasing alcohol consumption and reducing symptoms of withdrawal. Naltrexone, an opioid antagonist, cannot be prescribed to patients taking opioids (eg, methadone or buprenorphine); therefore, topirimate is a possibility for alcohol-dependent patients receiving treatment with opioids.

Nicotine

Cigarette smoking is so prevalent among HIV-infected drug users that it almost seems odd to encounter a patient who does not smoke. Advising patients to stop smoking does help, and encouragement to quit should be offered repeatedly. With regard to pharmacotherapy, nicotine replacement is effective. Bupropion doubles quit rates. Standard dosing of bupropion is 150 mg once daily for 3 days and then 150 mg twice daily for 7 to 12 weeks (Hurt et al, *N Engl J Med*, 1997). Because bupropion is metabolized by cytochrome P450 2D6, pharmacokinetic interactions with nelfinavir, ritonavir, and efavirenz need to be considered.

Varenicline, a partial nicotine receptor agonist, is FDA approved for the treatment of nicotine dependence and, in comparative studies, was better than bupropion (Gonzales et al, *JAMA*, 2006). The author finds it very effective, with patients generally choosing to either quit smoking or discontinue the medication (West et al, *Psychopharmacology* [Berl], 2008). However, there is a concern that varenicline may exacerbate serious neuropsychiatric symptoms (including the extremes of suicidality and homicidality), and its use requires circumspection and caution. Slow upward titration is necessary to minimize side effects.

Harm Reduction and Benefits of Physician Involvement

Those who work in HIV medicine are familiar with the concept of harm reduction as a goal of treatment. Sometimes the "success" of treating substance dependence will have to be, not the cessation of use, but the return of a patient to the next HIV-related appointment. Decreasing the frequency of adverse events related to a behavior is also a success, as is changing substance use behavior. A patient changing from heroin injection to sniffing can avoid endocarditis, for example. Of course, practitioners want harm removal—cessation of substance use—but if they can avoid at least some medical consequences of substance dependence and increase participation in HIV disease care in their patients, they have improved the overall health of their patients.

Harm reduction is crucial because drug addiction is a chronic illness with relapse rates similar to those in diabetes, hypertension, and asthma (Figure 3; McLellan et al, *JAMA*, 2000). In this regard, it should be remembered that primary care practitioners and society as a whole tend to moralize drug addiction, with relapse often seeming tantamount to confirmation of the categorical failure of the substance user. Instead, relapses should be seen and responded to in the same way as relapses in patients with hypertension,

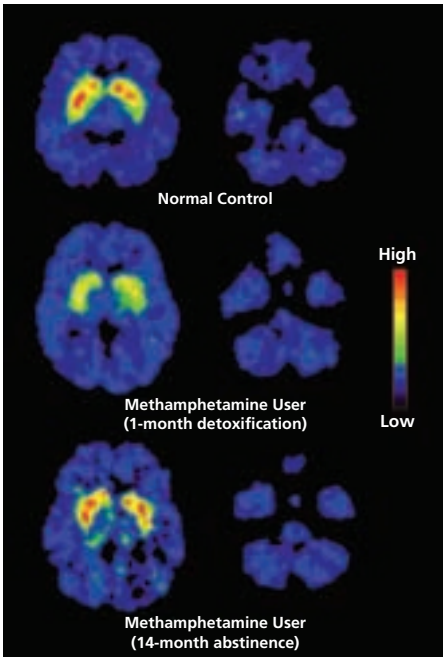

Figure **4**. Dopamine transporter recovery over a period of abstinence from methamphetamine (non–HIV-infected patient), as measured by brain images of the distribution volume of [C-11]*d-threo*-methylphenidate. Adapted with permission from Volkow et al, *J Neurosci*, 2001.

for example. Patients should be reminded of how much better they were feeling when they were taking their medications and of the health benefits that accrued during treatment, and they should be encouraged to resume treatment.

Practitioners never know when their efforts in extending medication-assisted treatment might tip the balance in favor of an improved health outcome such as helping the patients to stop using substances, reducing the adverse consequences of substance use, and improving patient participation and benefit in HIV care (Figure 4). Thus, HIV care practitioners would serve their patients well to prescribe pharmacotherapy for substance dependence. Similarly, advice and encouragement from physicians to stop smoking has proved to help patients quit smoking, and further benefits accrue when practitioners emphasize the importance of counseling for their patients and constantly encourage them to persist in it.

Presented by Dr Bruce in October 2009. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Bruce in January 2010.

Financial Disclosure: Dr Bruce has received grants and research support from Abbott Laboratories, Boehringer Ingelheim Pharmaceuticals, Inc, Merck & Co, Inc, and Reckitt Benckiser Pharmaceuticals, Inc.

Suggested Reading

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The following article in this issue is associated with CME credit:
Bruce RD. Medical interventions for addictions in the primary care setting. *Top HIV Med*. 2010;18(1):8-12

Objectives

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

- Discuss the broad effects of illicit substance use on brain circuits and motivational priorities in patients with HIV disease
- Identify different pharmacologic treatments useful for treating opioid, cocaine, methamphetamine, and alcohol dependence in patients with HIV infection
- Compare relapse rates of drug addiction with those of other chronic conditions
- Explain the concept of harm reduction as successful treatment of substance abuse in HIV-infected patients

Posttest Questions

Choose the single best answer to each of the questions below.

Question 1. Naltrexone is the most studied and consistently most efficacious pharmacotherapy for alcohol dependence. However, it cannot be used in patients taking methadone. Which 1 of the following medications has data that support its use for the treatment of alcohol dependence (though not currently approved by the US Food and Drug Administration [FDA] for alcohol dependence)?

❒ A. Gabapentin
❒ B. Topiramate
❒ C. Diazepam
❒ D. Modafinil

Question 2. Bupropion _____ cigarette quit rates compared with nicotine replacement therapy but is inferior to varenicline.

❒ A. Does not change
❒ B. Doubles
❒ C. Triples
❒ D. Quadruples

Question 3. Methadone is superior to buprenorphine in retention of patients in treatment for opioid dependence. Urine toxicology testing is often used to measure treatment outcome (although this use has been debated). In the testing data presented, opioid-free urine toxicology results for buprenorphine-maintained patients were _____ as good as those of methadone.

❒ A. One-half
❒ B. One-forth
❒ C. Equally
❒ D. Twice

Question 4. Current medications studied for treatment of cocaine dependence lack the efficacy of methadone or buprenorphine. However, 1 medication (approved by the FDA for alcohol dependence) has shown great promise in increasing dopamine levels through inhibition of dopamine beta-hydroxylase, thereby increasing dopamine levels in the brain and reducing craving for cocaine. This medication is:

❒ A. Topiramate
❒ B. Modafinil
❒ C. Disulfiram
❒ D. Bupropion

This CME activity is offered from **March 15, 2010,** to **March 15, 2012**. Participants who complete the activity posttest and submit the registration form are eligible to receive 0.5 CME credit. Physicians (MDs, DOs, and international equivalents) may receive CME credit for completing this activity. Nonphysician health care practitioners will receive a certificate of attendance.

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Intended Audience

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

Cases on the Web

www.iasusa.org/cow

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

Human Papillomavirus-Related Anal Squamous Cell Dysplasia and Carcinoma in HIV Infection

John Koeppe, MD, and Steven C. Johnson, MD
Level: All

Human papillomavirus (HPV) infection of the anus and HPV-related anal dysplasia are prevalent among HIV-infected persons. This COW activity discusses the risk of anal squamous cell carcinoma (SCC) in HIV-infected persons with anal dysplasia that is detected on cytologic screening. The use and limitations of digital rectal examination and anal Papanicolaou testing for screening of anal dysplasia and anal SCC are considered, and available treatment options for anal dysplasia are compared. The activity also discusses the use of condoms, HPV vaccines, and antiretroviral therapy to prevent anal dysplasia and anal SCC.

Common Drug Interactions in Patients Receiving Antiretroviral Therapy

John J. Faragon, PharmD, BCPS, David Condoluci, DO, and Cindy M. Hou, DO, MBA
Level: Basic

Drug interactions are an increasing challenge for practitioners who treat HIV-infected patients. To the typical 3-drug antiretroviral regimen may be added drugs for comorbid conditions and prophylaxis for opportunistic infections. Treatment is further complicated in patients in whom numerous antiretroviral regimens have failed, because such patients often require the use of more complex regimens to suppress HIV. This activity describes the effects of antiretroviral drugs and other drugs on the cytochrome P450 enzyme system and presents strategies for preventing interactions between antiretroviral drugs and selected coadministered drugs used in primary care settings.

Non–AIDS-Defining Cancers in Patients with HIV Infection

Roger J. Bedimo, MD, MS
Level: Advanced

Despite a substantial decline in the incidence of AIDS-defining cancers that has occurred with the use of antiretroviral therapy, the incidence of malignancies not known to be associated with immunosuppression, the non–AIDS-defining cancers, has increased. This presentation discusses changes in the spectrum of cancers among HIV-infected patients, the role immunodeficiency plays in the incidence of non–AIDS-defining cancers, and the management and prognosis of selected non–AIDS-defining cancers.

Management of an HIV-Infected Patient After Initial Antiretroviral Regimen Failure

Warangkana Sangchan, MD, and Lisa M. Chirch, MD
Level: Basic

Although the management of HIV has undergone dramatic improvement in recent years, failure of an initial antiretroviral regimen remains a common clinical challenge. In this activity, learners will identify the clinical and laboratory characteristics of an initial antiretroviral regimen failure and the possible causes of such failure. The presentation discusses management strategies for patients with first-regimen failure and appropriate antiretroviral regimens for treatment-experienced patients.

The Use of Chemokine Receptor Antagonists in Antiretroviral Treatment Failure

David M. Margolis, MD, and Gretchen Shaughnessy Arnoczy, MD
Level: Advanced

HIV engages in complex interactions with host cell-surface receptors to gain cellular entry and begin viral replication. The use of entry inhibitors such as chemokine receptor antagonists offers the potential for achieving virologic suppression in highly drug-experienced patients in whom this state was previously difficult to attain. This activity discusses the interpretation and the significance of HIV tropism assay results and the implementation of a chemokine receptor antagonist in a treatment-experienced patient with numerous treatment failures.

End-Stage Renal Disease in the HIV-Infected Patient

Christina M. Wyatt, MD
Level: Advanced

HIV-infected patients are at heightened risk of kidney disease related to HIV and coinfections and to the direct toxicity of antiretroviral therapy and concomitant medications. This expertly developed activity discusses current recommendations for the screening and management of chronic kidney disease (CKD) and end-stage renal disease (ESRD) in HIV-infected patients. Issues unique to the diagnosis and management of CKD in the HIV-infected are discussed as are criteria for identifying HIV-infected patients with ESRD who may be eligible for kidney transplantation.

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- **Use of Buprenorphine in HIV-Infected Patients – Level: Advanced**
- **Care of HIV-Infected Women During Pregnancy**

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Educational Programs of the International AIDS Society–USA

Established in 1992, the International AIDS Society–USA is a not-for-profit, HIV clinical specialist education organization. The mission of the International AIDS Society–USA is to improve the treatment, care, and quality of life of persons with HIV and AIDS through balanced, relevant, innovative, and state-of-the-art education and information for practitioners who are actively involved in HIV and AIDS care. The organization's educational activities are particularly intended to bridge clinical research and patient care.

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Tuesday, March 2, 2010
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Chair: Michael S. Saag, MD
Vice Chair: Jeffrey L. Lennox, MD

Chicago, IL
Monday, April 19, 2010
Marriott Chicago Downtown
Chair: John P. Phair, MD
Vice Chair: Paul A. Volberding, MD

Los Angeles, CA
Wednesday, March 10, 2010
Renaissance Hollywood
Chair: Ronald T. Mitsuyasu, MD
Vice Chair: Constance A. Benson, MD

San Francisco, CA
Monday, May 17, 2010
Grand Hyatt San Francisco
Chair: Robert T. Schooley, MD
Vice Chair: Stephen E. Follansbee, MD

New York, NY
Monday, March 22, 2010
Grand Hyatt New York
Chair: Gerald H. Friedland, MD
Vice Chair: Paul A. Volberding, MD

Washington, DC
Thursday, June 17, 2010
Capital Hilton
Chair: Henry Masur, MD
Vice Chair: Michael S. Saag, MD

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Washington, DC
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Special Contribution

Dermatologic Manifestations of HIV in Africa

Erin Huiras Amerson, MD, and Toby A. Maurer, MD

Dermatologic disease is common in HIV-infected individuals, and clinicians caring for patients with HIV infection or AIDS in Africa are routinely confronted with skin problems in their patients. Scarce access to dermatologic specialty care and limited educational resources describing the unique clinical characteristics of HIV-related skin disease can make diagnosing and treating skin diseases a challenge in Africa. This article describes common HIV-related dermatologic conditions in Africa and their differential diagnoses and includes treatment strategies that are likely to be available locally. It is not meant to be comprehensive but rather to serve as a practical resource to aid practitioners by providing images of common conditions and describing distinctive clinical presentations of common conditions.

The growing emphasis on global health and international volunteerism is increasing the demand for clinical education applicable across cultures and borders. The majority of HIV-infected individuals worldwide inhabit developing countries, yet medical research and literature regarding HIV- and AIDS-associated dermatologic disease have focused overwhelmingly on patterns of skin disease observed in white patients in resource-rich environments[1]. Differences in skin pigmentation, climate, hygiene, and other genetic, environmental, demographic, and behavioral variables contribute to unique clinical presentations and epidemiologic patterns of HIV-associated skin disease in Africa compared with North America and Europe. Examples of HIV-related skin diseases with divergent epidemiologic characteristics include the papular pruritic eruption (PPE) associated with HIV, Kaposi sarcoma (KS), cryptococcosis, and photodermatitis. Additionally, mutually common conditions such as seborrhea may have distinctive clinical presentations.

This article may be used as a practical guide to dermatologic disease in HIV-infected individuals in Africa, focusing on common diseases, as well as their differential diagnoses and treatments. It is not meant to be exhaustive, and given the dearth of medical literature regarding HIV dermatology in Africa, the majority of the information is based on the experience and expertise of the authors. Readers are encouraged to consult the literature and experts in the field for clarification or more information. In addition, local health regulations, drug approvals, and availabilities of specific treatments and procedures mentioned below vary considerably by region and are continuously evolving. Practitioners would benefit from consultation with others experienced with the local health care delivery system in resource-limited settings.

Papular Pruritic Eruption

PPE is a very common HIV-related skin disorder in tropical environments, including Africa. The underlying etiology probably reflects a hypersensitivity to insect bites,[2] hence the much higher incidence in tropical than temperate climates. PPE presents as extremely pruritic 0.2- to 1-cm papules that are darker than the patient's uninvolved skin (Figure 1). They may be excoriated from scratching and thickened or shiny from rubbing. The papules typically are numerous and predominate on the extremities, although the trunk may also be heavily involved. The diagnosis is made clinically and can be confirmed by skin biopsy when available. Immune reconstitution with antiretroviral therapy is the treatment of choice, but improvement typically takes at least 16 weeks; pruritus sometimes improves with use of potent topical steroids or topical capsaicin.

Figure **1**. Papular pruritic eruption of HIV. Thickened, hyperpigmented papules of less than 1 cm favoring the extremities.

Differential Diagnoses to Consider

Staphylococcal folliculitis. Bacterial folliculitis is a relatively common condition that may resemble PPE. Pruritus is variable, and lesions are typically fewer in number, are follicularly based, and may tend to be more concentrated on the upper trunk, upper arms, upper legs, and buttocks; pustules may be present. Treatment options include topical antiseptics (ie, chlorhexidine) and topical or oral antistaphylococcal antibiotics.

Eosinophilic folliculitis. Less common in Africa, eosinophilic folliculitis is a poorly understood HIV-related der-

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Figure **2**. Two examples of eosinophilic folliculitis. Itchy, follicularly based urticarial papules favoring the head, neck, and upper trunk.

matosis that, like PPE, is extremely pruritic. It may be differentiated from PPE based on its distribution, favoring the face, neck, scalp, and upper trunk (and almost never occurring below the nipple line). The papules are typically more urticarial and less shiny and hyperpigmented than in PPE (Figure 2). It often mimics acne clinically, but patients complain of severe itching, which is not a feature of acne. It may appear or worsen temporarily during immune reconstitution. Treatment of choice is antiretroviral therapy, but symptoms may be ameliorated with use of potent topical steroids or oral itraconazole 200 mg to 400 mg daily.

Scabies. Scabies infestation is very common and may be mistaken for PPE. Patients present with an intensely pruritic rash (Figure 3). The rash can appear papulonodular like PPE, pustular, eczematous, or even "crusted" in advanced HIV disease. Crusted, or "Norwegian," scabies manifests with a thick, powdery, grayish scale that is teeming with mites. Unlike PPE, scabies lesions tend to be clustered, sometimes with visible burrows, in the finger webs, around the waistline, and on the wrists and ankles. Clinicians should always examine the axillae, breasts, umbilicus, and penis in men and boys; involvement of these areas argues for a diagnosis of scabies over PPE or folliculitis. It is not unusual for the scratching to lead to bacterial superinfection. Commonly available treatment options include use of topical benzyl benzoate ester, 6% precipitated sulfur ointment, or oral ivermectin where available.

Figure **3**. Scabies. Extremely itchy papules clustered in the finger web spaces, with secondary staphylococcal superinfection.

Prurigo nodularis. Relatively common, prurigo nodularis presents with intensely pruritic, thickened, hyperpigmented, excoriated nodules (Figure 4). The nodules are larger (> 1 cm) and typically fewer in number (from 10-100 lesions) than in PPE. Prurigo nodules often start on the extremities and are bilateral and symmetric. With continued pruritus, they can become more widespread and appear on the trunk. Areas where patients cannot scratch, such as the midback, are spared. Prurigo nodularis results from intense scratching and does not have a single underlying etiology but may be secondary to other HIV-related dermatoses (such as photodermatitis, eczema, or PPE), underlying hepatitis C virus infection, renal failure, or lymphoma. Treatment should be directed at the underlying etiology, but symptoms can be treated with occlusion to provide physical protection from scratching, oral antihistamines, potent topical steroids, and topical capsaicin.

Figure **4**. Prurigo nodularis. Large (> 1 cm), symmetric, hyperpigmented nodules.

Seborrheic Dermatitis

As in the West, seborrhea is a very common skin disorder associated with HIV infection in Africa. Seborrheic dermatitis presents as a mildly itchy to nonitchy, scaly rash (Figure 5). Classically, the scalp, auditory canals, postauricular skin, and hair-bearing areas of the face and body (eyebrows, alar creases, beard, central chest, and axillae) are affected with erythema and "greasy" scale. However, in the authors' experience, seborrhea has a much more varied clinical presentation in Africa. It may spare the face altogether, affecting the scalp, ears, and skin folds such as the axillae, antecubital fossae, and inner thighs. It may also present as a rash with "powdery" scale and very little underlying erythema, favoring the scalp, ears, neck, shoulders, and back. It can occasionally present as erythroderma (full-body erythema and scale). There may be overlap with inverse psoriasis or eczema. Treatment depends on severity. Typically a combination of topical antifungal drugs directed at *Pityrosporum* yeast and low- to midpotency topical steroids for inflammation will lead to improvement.

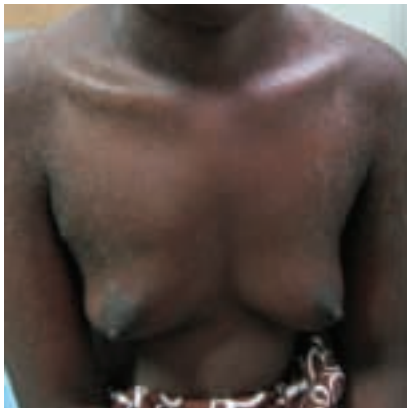

Figure **5**. Seborrheic dermatitis. Papules with fine, powdery scale distributed around the neck, shoulders, and axillae.

Figure **6**. Photodermatitis. Itching, scaling, and hyperpigmentation involving sun-exposed skin.

Figure **7**. Eczema. Chronic dry, scaly pruitic skin affecting the popliteal fossae.

Differential Diagnoses to Consider

Photodermatitis. Counterintuitively, dermatitis caused by sun exposure is more frequently observed in persons with darker skin types and is very common in HIV-infected persons in Africa. It can sometimes be quite difficult to differentiate from seborrhea. Photodermatitis presents as an itchy, scaly rash affecting the sun-exposed regions of the skin (the face, neck, "v" of the chest, dorsal arms, and sometimes lower legs and dorsal feet), sparing skin that is protected from the sun anatomically (eg, under the chin) or by clothing (Figure 6). This distribution is often clinically apparent when the patient's shirt is removed. HIV infection itself is photosensitizing, and many HIV-infected patients are taking photosensitizing drugs such as sulfonamides. Treatment includes immune restoration, sun-protective clothing such as hats and long-sleeved shirts, and potent topical steroids. Many of these patients earn a living working outside, and sunscreens are not widely available, making avoidance of sun exposure especially difficult. The authors do not recommend stopping sulfonamide prophylaxis because of photodermatitis; rather, these patients should be immune reconstituted to a level at which prophylaxis is no longer indicated.

Eczema. Advanced HIV disease causes dry skin, which can lead to eczema. Eczema is always pruritic and may be acute and weeping, or chronically dry and scaly (Figure 7). A background of xerosis (dry skin) is often present. Typically affected areas in adults include the eyelids, neck, flanks, hands, antecubital and popliteal fossae, and lower legs. Moister areas, such as the axillary skin, are typically spared. Treatment focuses on use of topical steroids and emollients and on avoidance of dessicating agents such as soaps. Emollients (such as petrolatum) should be applied immediately after bathing, while the skin is still moist.

Psoriasis. Psoriasis is relatively common in the HIV-infected population in Africa and may present with typical sharply demarcated, round, thick, scaly papules and plaques favoring the extensor extremities (Figure 8A). Atypical presentations, such as inverse psoriasis affecting the intertriginous areas and erythroderma, are common. There may be substantial overlap with seborrhea, with disease affecting the scalp, axillae, and inner thighs (Figure 8B). Destructive arthritis may be a feature. Most psoriasis will improve with antiretroviral therapy. Additional treatment is usually limited to use of topical steroids and short-contact anthralin therapy. Systemic agents are not routinely available or affordable, though this may vary by region. Psoriasis that has stabilized with antiretroviral therapy but suddenly flares may indicate a concomitant dermatologic condition such as scabies or staphylococcal infection, or it may be a marker of failure of current antiretroviral therapy. When pso-

Figure **8**. Psoriasis (A). Typical sharply demarcated erythematous plaques with "silvery" scale. Inverse psoriasis (B). Erythema and scale of the skin folds. There is overlap with seborrheic dermatitis.

riasis is suspected, other differential diagnoses to consider include reactive arthritis (Reiter syndrome) and secondary syphilis.

Drug Eruptions

With the roll-out of antiretroviral therapy in Africa, associated drug eruptions occur commonly. Two types of drug eruptions that deserve special mention are Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) and single or multiple fixed-drug eruptions (Figure 9).

Figure **9**. Toxic epidermal necrolysis. Note involvement of the lips and eyes and skin erosions with typical angular borders.

In the case of simple drug eruptions that are not life-threatening or incapacitating to the patient, clinicians may elect to "treat through" the symptoms with topical steroids and antihistamines. In this situation, patients should be monitored closely for the development of blisters, mucous membrane involvement, or systemic symptoms.

The overwhelming majority of serious drug eruptions in East Africa are caused by sulfonamides or nevirapine (Figure 10). Women starting nevirapine treatment at CD4+ counts above 250 cells/μL are particularly at risk of severe hypersensitivity reactions.[3,4] SJS/TEN is often easily recognized, as most patients present for care late in the course of the disease, with erosion

Figure **10**. Fixed drug eruption to sulfonamides. Erythema, erosion, and hyperpigmentation involving the vermillion border of the lip.

of mucous membranes (particularly the lower lip) and skin. Systemic steroid use is controversial; the authors do not recommend treatment with oral steroids unless used within the first 24 hours of symptom onset. Treatment is discontinuation of the offending drug as well as all other nonessential oral medications, and supportive care.

Fixed-drug eruptions typically present as strikingly round and sharply demarcated, intensely hyperpigmented patches (Figure 11). They may be single or multiple and located anywhere on the body, but the lips and genitals are frequent sites of involvement. The eruption may occur in the same place with each exposure or affect a new area of skin. In the authors' experience, the overwhelmingly common culprit is an antibiotic, most often a sulfonamide, although a host of other drugs may cause this eruption. In regions where antibiotics are available over the counter, fixed-drug eruptions occur frequently.

Figure **11**. Fixed drug eruption. Note the intense hyperpigmentation and strikingly round shape with an erythematous border. Blisters or erosions may be present.

Kaposi Sarcoma

Because of the endemic nature of human herpesvirus 8 in the region, KS is very common in HIV-infected persons in Africa. The demographics of KS in Africa are very different from those in the West, with men, women, and children all commonly affected (as opposed to western countries, where HIV-related KS is primarily a disease of men who have sex with men). KS classically presents as asymptomatic red-

Figure **12**. Kaposi sarcoma. Early lesions may present as hyperpigmented patches (A, foot) or red-purple patches (B, nose). More advanced lesions are red, purple, or brown nodules or plaques, often with accompanying "woody" lymphedema (C, inner thighs).

dish-purple to brown papules, plaques, or tumors favoring the head and neck (particularly the nasal tip, the palate, and around the neck), upper chest, genitals, inner thighs, lower legs, and soles of the feet (Figure 12).

Unfortunately, KS often presents in advanced stages in Africa, with accompanying lymphedema, aerodigestive tract involvement, or both. The cornerstone of treatment for KS currently remains early detection and antiretroviral therapy initiation, as liposomal doxorubicin/danorubicin chemotherapy is rarely available in Africa, and medical practitioners with experience and infrastructure to safely administer chemotherapy are few. The prognosis for individuals presenting with advanced disease is poor. Skin biopsy is necessary to differentiate KS from clinically similar HIV-related vascular proliferations such as bacillary angiomatosis (BA). Immune reconstitution may initially cause flaring of KS lesions, which can be life-threatening. Patients should be monitored closely during the initial phase of immune restoration.

Figure **13**. Two examples of bacillary angiomatosis. Vascular papules and nodules are difficult to differentiate clinically from Kaposi sarcoma.

Differential Diagnoses to Consider

Bacillary angiomatosis. Although only sparsely reported in Africa, BA is probably more common than the literature reflects because of a lack of widely available skin biopsy and histopathology services. Like KS, it most often presents as solitary or multiple asymptomatic red-purple bumps (Figure 13). BA may also affect bone and viscera and can be fatal if untreated. Diagnosis is confirmed by a silver stain of a skin biopsy sample that reflects the presence of the causative organism, *Bartonella henselae* or *B quintana*. Treatment consists of at least 6 weeks of oral erythromycin or doxycycline. For visceral involvement, 3 months of antibiotic treatment should be considered.

Lymphoma. Although non-Hodgkin lymphoma presents in the skin relatively rarely, cutaneous metastases can present as red to purple papules or plaques in the skin, often with a more translucent or "jellylike" appearance than KS (Figure 14). The diagnosis can be made by skin biopsy.

Figure **14**. B-cell lymphoma. This individual exhibits typical lesions of nodular Kaposi sarcoma on the medial thigh, with a more translucent red-purple plaque overlying an enlarged inguinal lymph node representing lymphoma cutis.

Others. Other disorders that can mimic KS in dark-skinned patients include pyogenic granuloma, warts, scars, postinflammatory hyperpigmentation, lichen planus (Figure 15), and inflammatory tinea facei or tinea corporis.

Figure **15**. Lichen planus. Purple papules with overlying fine white scale. Note the linear arrangement of papules where the skin was scratched; this is known as the Koebner phenomenon and does not occur in Kaposi sarcoma.

This underscores the importance of skin biopsy in confirming the diagnosis of KS, especially before administering chemotherapy.

Molluscum Contagiosum

Molluscum contagiosum (MC) is very common in HIV-infected persons, par-

Figure **16**. A single molluscum and hundreds of flat warts in an HIV-infected child. Note the umbilicated center of molluscum. Flat warts may also exhibit the Koebner phenomenon, appearing in strikingly linear arrangements.

ticularly pediatric patients, in Africa (Figure 16). MC is caused by a poxvirus. It presents with dome-shaped, umbilicated papules, typically 3 mm to 8 mm, although giant lesions can occur in advanced HIV disease. Antiretroviral therapy is the mainstay of treatment, but curettage or silver nitrate treatment may also be used.

Differential Diagnosis to Consider

Cryptococcosis. Disseminated cryptococcal disease can present in the skin, often preceding or simultaneous with the onset of meningitis symptoms. Clinically, the lesions resemble MC, although the central umbilication often has a hemorrhagic crust. The skin lesions of cryptococcosis are often eruptive, as opposed to the slower, insidious onset of MC (Figure 17). Clinicians should maintain a high level of suspicion for cutaneous cryptococcosis in Africa, where cryptococcal disease is very prevalent, particularly if the lesions appear over a short time course.

Figure **17**. Cryptococcosis. Eruptive appearance of numerous umbilicated papules on the face.

The presence of cryptococcal skin lesions indicates a systemic infection, and a serum cryptococcal antigen test result will be positive. Systemic antifungal therapy should be initiated.

Warts

Viral warts, both genital and nongenital, are very common in Africa (Figure 16). Particularly in pediatric patients, hundreds of flat warts are a frequent, and stigmatizing, finding that may or may not improve with antiretroviral therapy. Cryotherapy, the standard wart treatment in developed countries, is generally not available. Large genital lesions may be treated with 25% podophyllin, which is painted on the warts and washed off in 4 hours to 6 hours, and nongenital warts may be treated with salicylic acid preparations. Genital warts should be monitored for rapidly growing firm nodules or ulcers that may indicate human papillomavirus-induced squamous cell carcinoma.

Herpes Simplex Virus and Varicella-Zoster Virus Infections

Infections with herpes simplex virus and varicella-zoster virus are quite common in Africa and most often present in the typical fashion. Large, chronic ulcerations of the face, genitals, or buttocks due to herpes simplex virus infection are frequent in patients with advanced HIV disease (Figure 18). A "scalloped" border to a chronic ulceration can be a clue to the diagnosis. Oral acyclovir treatment is generally available, whereas intravenous acyclovir can be difficult to obtain, and alternative antiherpetic drugs are not widely available.

Figure **18**. Herpes simplex virus infection. A large, chronic, nonhealing crusted ulceration in an HIV-infected patient.

Varicella-zoster virus infection in the V1 distribution (involving the eye) may eventuate in blindness. Intravenous acyclovir treatment is recommended in this case, as the absorption is superior to the oral route. Postherpetic neuralgia is less of a problem in patients with HIV, with the exception of varicella-zoster virus infection in the V1 region (Figure 19).

Figure **19**. Varicella-zoster virus infection affecting the V1 dermatome.

Tinea

Tinea is a universally common skin problem in HIV-infected patients. Typical tinea has an inflammatory, scaly border; in darkly pigmented patients, the area of central "clearing" is usually hyperpigmented (Figure 20). Common locations include the hands, feet, and lower back or buttocks. Special considerations in Africa include tinea incogni-

Figure **20**. Tinea facei. Note the active inflammatory border and central postinflammatory hyperpigmentation. Tinea facei often lacks scale at the active border; elsewhere on the body, the border should be scaly.

to, a noninflammatory presentation of tinea caused by use of widely available over-the-counter skin products that contain potent steroids. Topical antifungal drugs can be used for localized disease, whereas oral antifungal drugs such as griseofulvin or ketoconazole may be necessary for widespread infection or involvement of hair follicles (majocchi granuloma), indicated by follicular papules or pustules. Tinea capitis requires treatment with oral antifungal drugs for a minimum of 6 weeks.

Other Considerations

In addition to familiarity with the specific entities described above, the clinician with less experience with dermatologic disease in darkly pigmented persons will benefit from an understanding of a few general principles. First, erythema may be difficult to appreciate and may appear gray, violet, or simply hyperpigmented. Additionally, darkly pigmented individuals commonly experience a phenomenon called postinflammatory pigment alteration (PIPA) in response to underlying inflammation, regardless of the cause. Hyperpigmentation, hypopigmentation, or both may occur. There is no treatment for PIPA, aside from treating the underlying condition and allowing the pigmentary changes to resolve. Also, bacterial superinfection with *Staphylococcus* or *Streptococcus* species, known as "impetiginization," is extraordinarily common with all pruritic skin diseases in Africa. This presents as golden or honey-colored crusting and often superficial erosion of skin. Although primary impetigo can occur, patients should be examined for an underlying pruritic disease such as eczema, scabies, or insect bites.

Financial disclosure: Dr Amerson and Dr Maurer have no relevant financial affiliations to disclose.

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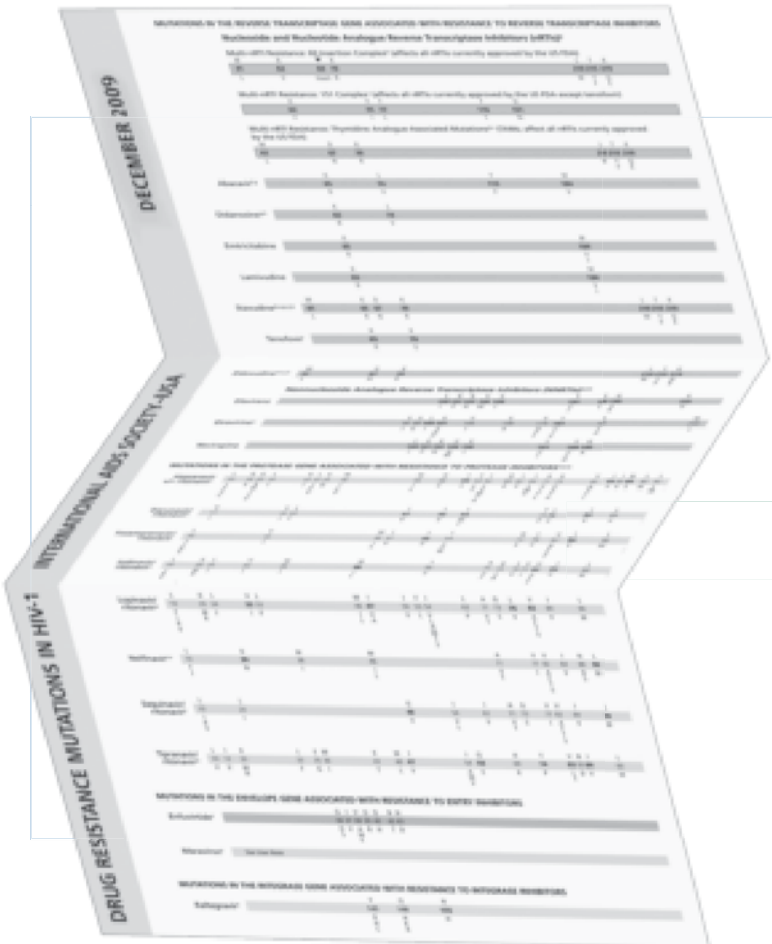

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