

Topics in HIV Medicine®

A publication of the International AIDS Society–USA

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Joel E. Gallant, MD, MPH

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About This Issue

This issue features 3 *Perspective* articles and one *Commentary* article. The first *Perspective* article summarizes a presentation given by David B. Clifford, MD, at an International AIDS Society–USA Continuing Medical Education course in New York in October 2007, which discussed the continuing high rate of HIV-associated neurocognitive disturbances in patients, despite the ability to suppress viral replication with antiretroviral therapy. A second *Perspective* article, based on a presentation at the same IAS-USA course by Joel E. Gallant, MD, MPH, discusses current thinking on when to initiate antiretroviral treatment, including recommendations for immediate treatment in selected patients. The final *Perspective* article, based on a presentation made by Carl Grunfeld, MD, PhD, at the 10th Annual Ryan White HIV/AIDS Program Clinical Update held in Phoenix in June 2007, reviews the causes of insulin resistance in HIV infection, including not only the direct effects of antiretroviral drugs but also factors such as aging and restoration to health accompanied by fat accumulation. The *Commentary* article, based on a presentation by Andrew F. Angelino, MD, at the same Clinical Update Program in June 2007, notes our society's inadequate response to major factors fueling the epidemic—the high frequency of mental disorders in the HIV-infected, homeless, and corrections populations and associations of these populations both with risk behaviors for acquiring and transmitting infection and with poorer outcome as the result of failure to seek or adhere to appropriate treatment.

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Perspective

When to Start Antiretroviral Therapy: A Swinging Pendulum?

Although early initiation of antiretroviral treatment has long been associated with some benefit over later initiation, the magnitude of the benefit is becoming better defined with longer follow-up of large numbers of patients in cohort studies. These benefits have become more evident in part because of improvements in efficacy, tolerability, and convenience of antiretroviral treatment regimens. The benefits also reflect growing recognition of the effect of such treatment in reducing risk of both HIV-related and non-HIV-related complications that are not associated with low CD4+ cell count. On balance, currently available information supports using a CD4+ count of 350 cells/ μ L as a general threshold for initiating treatment, with immediate treatment warranted for selected patients, including those with conditions for which antiretroviral therapy is the best or only treatment. This article summarizes a presentation on when to initiate antiretroviral therapy made by Joel E. Gallant, MD, MPH, at an International AIDS Society–USA Continuing Medical Education course in New York in October 2007. The original presentation is available as a Webcast at www.iasusa.org.

Since the advent of antiretroviral treatment, the recommended CD4+ cell count threshold for starting therapy has steadily declined, with 2006 recommendations of the US Department of Health and Human Services (DHHS), the International AIDS Society–USA, and the British HIV Society all generally indicating a threshold of 200 cells/ μ L for initiating treatment in asymptomatic patients. The rationale for later treatment included the acknowledgment that eradication of HIV is not a realistic goal of antiretroviral therapy and recognition of both the long-term toxicities of treatment and the absence of data indicating that earlier treatment provided marked benefits. More recently, however, accumulating information on the effects of earlier versus later treatment has resulted in a shift toward earlier initiation of antiretroviral therapy.

Easier, More Potent, Less Toxic Therapy

Newer antiretroviral regimens are less complex, better tolerated, and more po-

tent than older regimens. This combination of factors appears to be reflected in the higher rates of achievement and maintenance of plasma HIV RNA levels below 50 copies/mL at 48 weeks in more

recent clinical trials. As shown in Figure 1, outcomes with ritonavir-boosted protease inhibitors (PIs) and nonnucleoside analogue reverse transcriptase inhibitors (NNRTIs) as part of triple therapy (ie, newer regimens) are more effective than those with older regimens that used unboosted PIs and nucleoside analogue reverse transcriptase inhibitors (nRTIs) (Bartlett et al, *AIDS*, 2006). Similar information has come from observational cohorts. For example, data from patients in 5 clinic cohorts in Europe and Canada beginning treatment from 1996 to 2002 show greater increases in median CD4+ cell count and reduced frequency of virologic failure during the first year of treatment over this period (Figure 2); most cases of virologic failure in the more recent years resulted from loss to follow-up or treatment discontinuation rather than loss of antiviral efficacy (Lampe et al, *Arch Intern Med*, 2006).

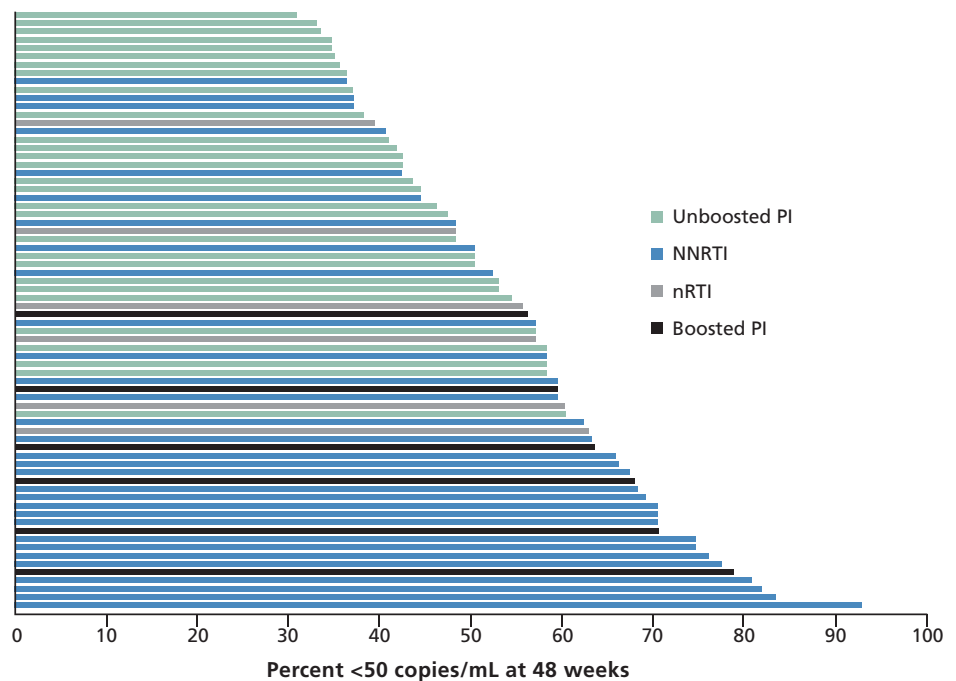


Figure 1. Percent of patients with plasma HIV RNA levels below 50 copies/mL at 48 weeks with antiretroviral regimens containing indicated components. Unboosted indicates without ritonavir; NNRTI, nonnucleoside analogue reverse transcriptase inhibitor; nRTI, nucleoside analogue reverse transcriptase inhibitor; boosted, with low-dose ritonavir added. Adapted from Bartlett et al, *AIDS*, 2006.

Dr Gallant is a Professor of Medicine and Epidemiology at The Johns Hopkins University School of Medicine and Associate Director of the Johns Hopkins AIDS Service in Baltimore, Maryland.

Benefits of Earlier Treatment Initiation in Cohort Studies

With longer follow-up and larger sample sizes, cohort studies have begun to yield a consistent picture of benefits from earlier initiation of antiretroviral therapy. Data from the Antiretroviral Therapy Cohort Collaborative, which involved 10,855 patients (excluding injection drug users) and more than 61,000 person-years of follow-up, showed reduced risk for AIDS or death among patients initiating treatment at CD4+ counts of 351 to 500 cells/ μ L compared with those starting at lower counts, with the benefit becoming more pronounced over time (Figure 3). The hazard ratio (HR) for AIDS was 3.68 (95% confidence interval [CI], 3.01-4.51) for patients starting treatment at CD4+ counts below 200 cells/ μ L versus counts of 201 to 350 cells/ μ L and 1.52 (95% CI, 1.10-2.10) for patients with counts below 350 cells/ μ L versus 351 to 500 cells/ μ L. Risk for AIDS or death was significantly increased in patients beginning treatment at counts below 200 cells/ μ L versus 201 to 350 cells/ μ L (HR, 2.93; 95% CI, 2.41-3.57) and nonsignificantly increased for those starting at counts less than 350 cells/ μ L versus 351 to 500 cells/ μ L (HR, 1.26; 95% CI, 0.94-1.68) (May et al, *AIDS*, 2007).

Similarly, data from 4421 patients in the HIV Outpatient Study (HOPS) cohort show incremental reductions in incidence of both opportunistic infections and mortality with treatment initiated at various CD4+ counts including 200 to 349 cells/ μ L, 350 to 499 cells/ μ L, and greater than or equal to 500 cells/ μ L (Figure 3). Major mutations were 50% less likely to occur in patients starting treatment at counts above 350 cells/ μ L versus at counts below 200 cells/ μ L, despite greater treatment exposure among the former, and more NRTI toxicity (anemia, neuropathy, renal insufficiency) occurred with initiation of antiretroviral therapy at lower CD4+ counts (Lichtenstein et al, *CROI*, 2006). Data on 280 patients with virologic suppression for up to 6 years in the Johns Hopkins HIV cohort show that CD4+ counts returned to near-normal levels only in patients with pretreatment counts

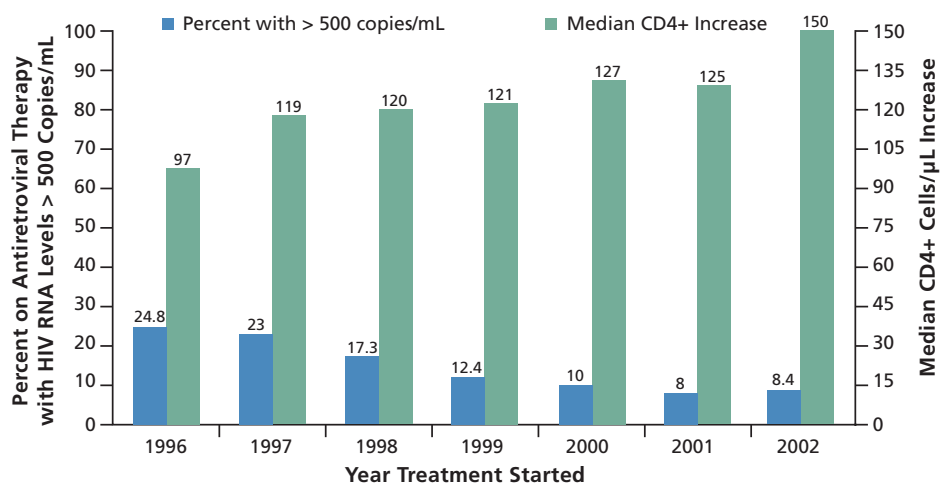


Figure 2. Rates of virologic failure and median CD4+ cell count increases during the first year of antiretroviral therapy by year of starting treatment in 5 clinic cohorts. Adapted from Lampe et al, *Arch Intern Med*, 2006.

above 350 cells/ μ L (Figure 3). The rate of progression to AIDS or death was statistically significantly higher over time in patients with pretreatment counts below 200 and from 201 to 350 cells/ μ L versus in those with counts above 350 cells/ μ L. Overall, AIDS developed in 1.5% of patients starting at counts above 350 cells/ μ L, in 12% of those starting at 201 to 350 cells/ μ L, and in 13% of those starting below 200 cells/ μ L (Moore and Keruly, *Clin Infect Dis*, 2007).

Decreased Transmission Risk

Suppressive therapy begun earlier might reduce HIV transmission. The ability to reduce transmission risk via suppressive therapy has been demonstrated in the setting of perinatal transmission. Considerable evidence from observational studies indicates that viral load is strongly correlated with transmission risk; for example, a study among HIV-discordant couples in Rakai, Uganda, showed that transmission risk was exceedingly low when the infected partner had a plasma HIV RNA level below 1700 copies/mL, with risk incrementally increasing with levels of 1700 to 12,500 copies/mL, 12,500 to 38,500 copies/mL, and above 35,000 copies/mL (with the presence of genital ulcer disease markedly increasing risk in each of these categories) (Gray et al, *Lancet*, 2001).

An ongoing multinational trial is examining whether immediate early therapy in infected individuals in discordant couples reduces transmission risk compared with therapy started according to current guidelines.

Preservation of R5-tropic Virus

Virus with R5-coreceptor tropism is associated with less rapid disease progression than virus with X4-coreceptor tropism or dual/mixed-tropic virus, and R5-tropic virus predominates in earlier infection. Although the precise mechanisms of the switch in tropism are unclear, the switch may be related to nadir CD4+ cell count, and earlier antiretroviral treatment might prevent or delay the switch. Screening in the MERIT study showed that among 1428 antiretroviral therapy-naïve patients, 85% had R5-tropic virus, 0.3% had X4-tropic virus, and 14.7% had dual/mixed-tropic virus, whereas among 2560 antiretroviral therapy-experienced patients screening for the MOTIVATE 1 and 2 studies, the respective proportions were 56%, 2.6%, and 41.4% (Coakley et al, International Workshop Targeting HIV Entry, 2006).

A recent example of the effect of tropism is provided by data from 294 antiretroviral therapy-naïve patients with baseline CD4+ counts above 450 cells/ μ L and plasma HIV RNA levels

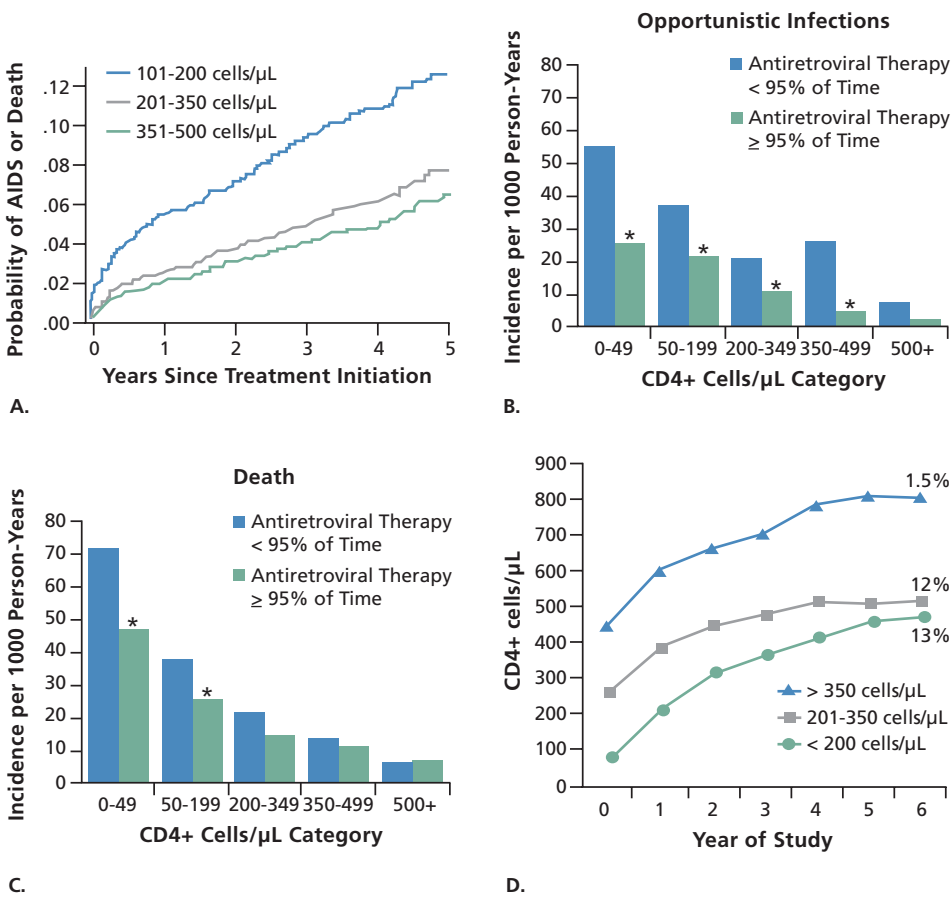


Figure 3. A: Cumulative probability of AIDS or death by initial CD4+ cell count from the Antiretroviral Therapy Cohort Collaboration. Adapted from May et al, *AIDS*, 2007. Incidence of opportunistic infections (B) and death (C) according to initial CD4+ count (and percent of time on antiretroviral treatment) in the HIV Outpatient Study (HOPS) cohort. Asterisks indicate data for which the difference based on percent of antiretroviral use is statistically significant at $P < .05$. Adapted from Lichtenstein, CROI, 2006. D: CD4+ count increase according to initial CD4+ count in patients with viral suppression on antiretroviral therapy in the Johns Hopkins HIV cohort. Percents are percent of patients in each group who developed AIDS; $P < .05$ for the top curve data compared with the bottom curve data. Adapted from Moore and Keruly, *Clin Infect Dis*, 2007.

above 1000 copies/mL in the Community Program for Clinical Research on AIDS (CPCRA) 060 study. Of these, 262 patients (89%) had R5-tropic virus, and 32 (11%) had dual/mixed-tropic virus. The relative risk of progression, defined as CD4+ count less than 350 cells/μL, initiation of antiretroviral therapy, or death, was 2.11 (95% CI, 1.25-3.57; $P = .005$) for dual/mixed- versus R5-tropic virus; the significant effect of tropism in predicting progression was independent of viral load and CD4+ cell count (Goetz et al, *IAC*, 2007). In addition to potentially slowing progression by preventing the tropism switch, earlier initiation of antiretroviral treat-

ment might also thus preserve the utility of maraviroc or other CCR5-antagonist antiretroviral drugs.

Cost-effectiveness

Published data support the notion that early initiation of antiretroviral therapy is cost-effective. Markov modeling using the Johns Hopkins Moore Clinic HIV database showed that beginning treatment at CD4+ counts greater than 350 cells/μL versus at counts of 200 to 350 cells/μL resulted in an incremental cost per quality-adjusted life-year (QALY) gained of \$31,226, which is well within the limits of current standards of cost-

effectiveness, representing greater cost-effectiveness than such widely accepted interventions as coronary bypass, hemodialysis, screening mammograms, and mandatory seat belt laws (Mauskopf et al, *JAIDS*, 2005).

Prevention of Specific Complications of HIV Infection

Some complications of HIV infection are more closely related to low CD4+ count than others. Thus, use of a CD4+ count of 200 cells/μL as a threshold for treatment is effective in preventing such complications as *Pneumocystis jiroveci* (formerly *Pneumocystis carinii*) pneumonia, toxoplasmosis, cryptosporidiosis, and *Mycobacterium avium* complex. However, other complications, including neurocognitive impairment, non-Hodgkin's lymphoma, peripheral neuropathy, human papilloma virus-associated dysplasia/cancer, Kaposi's sarcoma, and HIV-associated nephropathy, are less dependent on CD4+ count. These conditions can be observed at high CD4+ cell counts, frequently in the setting of persistent high viral load, and earlier initiation of treatment might thus reduce risk for these complications.

Prevention of Non-opportunistic Complications

Earlier treatment might also prevent non-opportunistic complications associated with HIV-related immunosuppression. Numerous recent studies have shown that non-opportunistic conditions, including various bacterial infections, liver disease, kidney disease, and non-AIDS-defining malignancies, occur at higher and CD4+ count-dependent rates in individuals with HIV infection. In the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study of more than 23,000 patients with HIV infection, 1248 patients (5.4%) died between 2000 and 2004, of whom 82% were on antiretroviral therapy. Figure 4 shows that both HIV-associated and non-HIV-associated mortality were related to CD4+ cell count in these patients (Weber et al, CROI, 2005).

Similarly, data on 1397 patients starting antiretroviral therapy in the

Flexible Initial Retroviral Suppressive Therapies (FIRST) study showed that the incidence of non-opportunistic diseases declined with higher CD4+ cell count (Figure 4), with the most recent CD4+ count being an independent predictor of risk for non-opportunistic disease. At CD4+ counts above 200 cells/ μ L, non-opportunistic disease events accounted for more morbidity and mortality than did opportunistic disease (Baker et al, CROI, 2007).

The Strategies for Management of Antiretroviral Therapy (SMART) trial randomized patients on antiretroviral therapy to continue treatment or to stop when the CD4+ count was above 350 cells/ μ L and resume treatment when the count dropped to 250 cells/ μ L. The trial showed that interrupting therapy was associated with a statistically significantly increased risk of opportunistic infection or death (HR, 2.6), opportunistic infection (HR, 3.6), or non-opportunistic infection death (HR, 1.8) (SMART Study Group et al, *N Engl J Med*, 2006). Analysis of cardiovascular outcomes in the trial showed that interrupting treatment was associated with an increased risk of the composite of clinical myocardial infarction (MI), silent MI, coronary disease requiring invasive procedure, or cardiovascular death (relative hazard [RH], 1.57;

$P = .05$); the foregoing plus peripheral vascular disease, heart failure, or coronary disease requiring medication (RH, 1.49; $P = .03$); and the foregoing plus unobserved death from unknown cause (RH, 1.58; $P = .009$). These findings occurred in the context of a significantly higher ratio of total cholesterol to high-density lipoprotein cholesterol in the treatment-interruption group (Phillips et al, CROI, 2007).

A subset analysis in SMART among patients who were either antiretroviral therapy-naïve or not receiving antiretroviral therapy at randomization to immediate (ie, continuous) treatment ($n = 249$, 131 antiretroviral therapy-naïve) or deferred (ie, interrupted) treatment ($n = 228$, 118 antiretroviral therapy-naïve) showed that deferred treatment was associated with a 5-fold increased risk of the composite of opportunistic infection, opportunistic infection or death, or serious non-AIDS events (HR, 5.08; $P = .001$) (Figure 4) (Emery, IAC, 2007). In the Concerted Action on Seroconversion to AIDS and Death in Europe (CASCADE) study, non-AIDS-related deaths accounted for more than 50% of 597 deaths in 9858 patients with a median follow-up period of 8 years from seroconversion; current and nadir CD4+ count and time with CD4+ count below 350 cells/ μ L were associated with both AIDS deaths

and non-AIDS deaths such as infections, liver disease, or malignancy (Marin et al, IAC, 2007).

Potential Immunologic Benefits

Naïve and memory CD4+ cells reside in gut-associated lymphoid tissue. Studies of the pathogenesis of acute HIV infection indicate that gut-associated CD4+ cells decline dramatically in early infection, and the hypothesis is that microbial translocation and immune stimulation in the gut drive the continuing loss of CD4+ cells. Earlier (asymptomatic) treatment with antiretroviral therapy is associated with significantly greater increases in the central memory CD4+ cell populations of Peyer's patches than is late (symptomatic) treatment (Estes et al, CROI, 2007). Thus, earlier treatment may lead to improved immune reconstitution. It is unclear, however, at what point early treatment would need to begin to derive clinical benefit in this process and what the precise clinical consequences of such intervention might be.

Special Considerations: Treatment Above 350 CD4+ Cells/ μ L

In contrast to previous versions of the DHHS guidelines, which included cat-

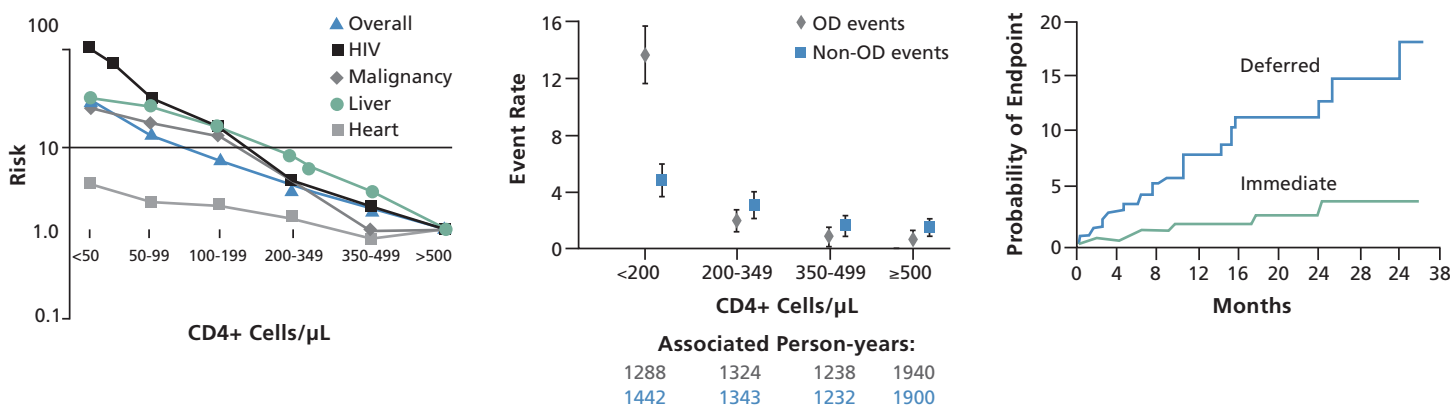


Figure 4. Left: Relative risk of HIV-related mortality (HIV) and non-HIV-related mortality (malignancy, liver, heart) by CD4+ count <50 versus >500 cells/ μ L in the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study. Adapted from Weber et al, CROI, 2005. Center: Rates (events per 100 person-years of observation) of opportunistic disease (OD) and non-OD events by CD4+ count in the Flexible Initial Retroviral Suppressive Therapies (FIRST) study. Adapted from Baker et al, CROI, 2007. Right: Risk for reaching a composite endpoint of opportunistic infection, opportunistic infection or death, or serious non-AIDS event among patients with deferred versus immediate antiretroviral therapy in a subset study in the Strategies for Management of Antiretroviral Therapy (SMART) trial (hazard ratio, 5.08; 95% CI, 1.91-13.5; $P = .001$). Adapted from Emery, IAC, 2007.

egories of patients who should not be treated, the current guidelines point out that antiretroviral therapy is indicated or could be considered in some patients whose count does not fall below the 350 cells/ μ L threshold. The current guidelines (US DHHS, <http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf>) recommend initiation of antiretroviral therapy at any CD4+ cell count in patients with HIV/HBV coinfection who need treatment for HBV. It is easier to treat both infections simultaneously (using dual-therapy against HBV, tenofovir plus either emtricitabine or lamivudine plus an NNRTI or boosted PI) than it is to attempt to treat either virus alone with drugs that are active against only 1 of the 2 viruses.

The only effective treatment for HIV-associated nephropathy (HIVAN) is antiretroviral therapy. For that reason, the DHHS guidelines also recommend initiation of antiretroviral therapy regardless of CD4+ cell count in patients in whom HIVAN is diagnosed.

Pregnant women should also receive antiretroviral therapy regardless of CD4+ cell count to prevent mother-to-child transmission. Therapy can be stopped after delivery, although in light of the findings of the SMART study, some experts would consider continuing therapy in a woman who was doing well on a suppressive regimen.

Other factors that might prompt consideration of earlier therapy might include rate of CD4+ decline, a high baseline viral load, older age, or concerns about prevention of HIV transmission, as for patients with seronegative partners or patients engaging in ongoing high-risk activity.

Progression of hepatitis C virus (HCV) disease is associated with CD4+ count in coinfecting persons, so there is some support for earlier treatment of HIV infection in such patients. This remains controversial, however, given the lack of clinical data and the concern over the potential hepatotoxicity of some antiretroviral drugs. Nevertheless, early antiretroviral therapy could be considered for highly motivated HIV patients who need treatment for HCV disease as well.

Caveats and Concerns

Much of the data supporting earlier initiation of antiretroviral treatment comes from observational studies. One obvious problem with regard to interpreting data is that patients enrolled in such studies who start treatment with advanced disease may do poorly for reasons unrelated to CD4+ cell count (eg, disenfranchisement, illicit drug use, mental illness, homelessness). By the same token, those beginning treatment early are more likely to be highly motivated patients who adhere to therapy. It is unclear whether we will ever have data from a randomized, controlled trial of this issue. A large trial is currently being planned. However, prior attempts to enroll patients in such trials have failed, in part because of the reluctance on the part of both clinicians and patients to leave such an important decision to randomization. The available observational data, while not definitive, provide compelling support for earlier therapy. A large, randomized trial would also be expensive and time-consuming, and it is unclear whether the questions asked or the

CD4+ count thresholds examined in such a trial would still be considered relevant by the time the results became available.

A sobering consideration in this discussion is that for much of the HIV-infected population, a recommendation to start antiretroviral treatment at a CD4+ count of 350 cells/ μ L means little in terms of actual practice. Figure 5 shows CD4+ count at the start of treatment in various worldwide locales for 2003 through 2005, indicating that treatment in many settings is routinely begun at more advanced stages of disease. Frequently, US practitioners first encounter patients when they seek treatment for an acute opportunistic infection, at which point their CD4+ count may be less than 100 cells/ μ L rather than above 350 cells/ μ L. Indeed, the starting CD4+ count at first visit in the United States is below that of many developed nations, indicating the true state of HIV health care in this country. It is hoped that implementation of the new CDC recommendations for routine HIV testing will result in earlier diagnosis of HIV infection, allowing more infected individuals to benefit from earlier therapy.

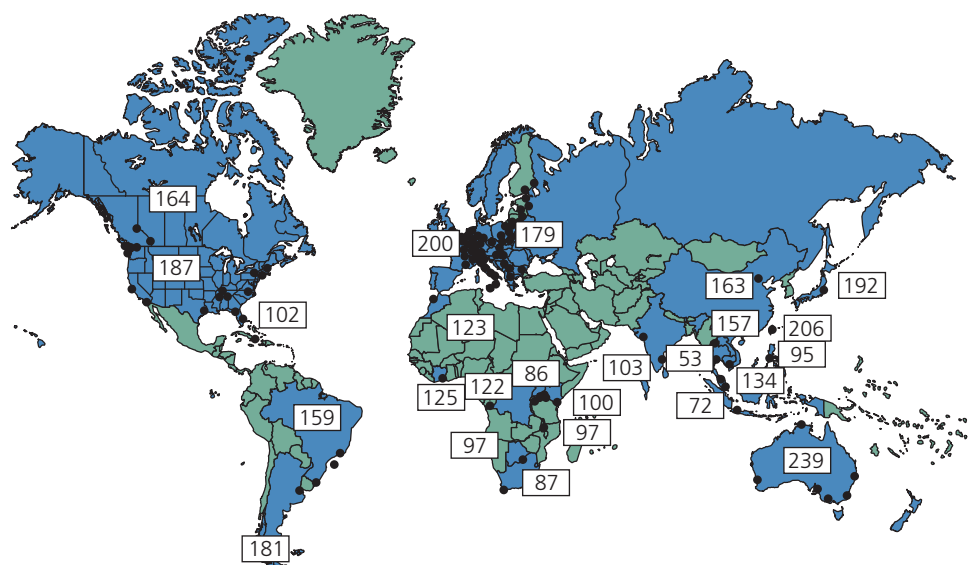


Figure 5. CD4+ counts (cells/ μ L) at initiation of antiretroviral therapy in 2003 to 2005. Since 2000, CD4+ count at initiation of treatment has increased in sub-Saharan Africa from 50 to 100 cells/ μ L, has remained stable in developed countries at approximately 150 to 200 cells/ μ L, and is lower in the United States than in many other resource-rich countries. Adapted from Egger, CROI, 2007.

Initiating Antiretroviral Therapy in the Setting of Acute Opportunistic Infections

Antiretroviral therapy should be started immediately in patients with conditions for which it is the best or only therapy, such as progressive multifocal leukoencephalopathy, HIV-associated dementia, HIV-associated nephropathy, Kaposi's sarcoma, cryptosporidiosis, or microsporidiosis, and in patients with conditions for which a higher CD4+ cell count improves prognosis, such as primary central nervous system lymphoma or non-Hodgkin's lymphoma. There is also evidence that early initiation of antiretroviral therapy may improve outcome in patients with *Pneumocystis jirovecii* pneumonia (Zolopa et al, CROI, 2008). The data are less clear for other opportunistic infections. For some, such as tuberculosis, *Mycobacterium avium* complex, and cryptococcal meningitis, concerns about the risk of delayed antiretroviral therapy must be balanced against the risk of the immune reconstitution inflammatory syndrome when antiretroviral therapy and treatment of the opportunistic infection are initiated simultaneously. Simultaneous initiation of antiretroviral therapy and therapy for tuberculosis can also lead to overlapping drug toxicity and important drug interactions between rifamycins and antiretroviral agents.

Bottom Line: When to Start

Treatment should be started in any patient with a CD4+ count below 350 cells/ μ L, any patient with HIV and HBV coinfection requiring treatment for HBV infection, pregnant patients, and patients with HIVAN and other conditions that require antiretroviral therapy, as noted above. Treatment might also be considered at CD4+ counts above 350 cells/ μ L in selected patients with rapid CD4+ count declines, patients with high viral loads, infected patients with HIV-seronegative partners, and infected patients engaging in high-risk behaviors.

There is clearly a possibility that future guidelines will recommend even earlier treatment. Given the recent improvements in the risk:benefit ratio of

antiretroviral therapy, a case could be made for initiating antiretroviral therapy at any CD4+ count in a motivated patient who wants to be treated and has evidence of HIV progression. This approach is not currently the standard of care, however.

Treatment can be deferred in patients with some acute opportunistic infections, as noted above; long-term non-progressors or those with high CD4+ count and low viral load who might fit into this category after further follow-up; patients who are not ready or motivated to start treatment or not likely to be adherent; and patients with extensive transmitted resistance and few treatment options who are not in immediate need of antiretroviral therapy.

Presented by Dr Gallant, in October 2007. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Gallant in May 2008.

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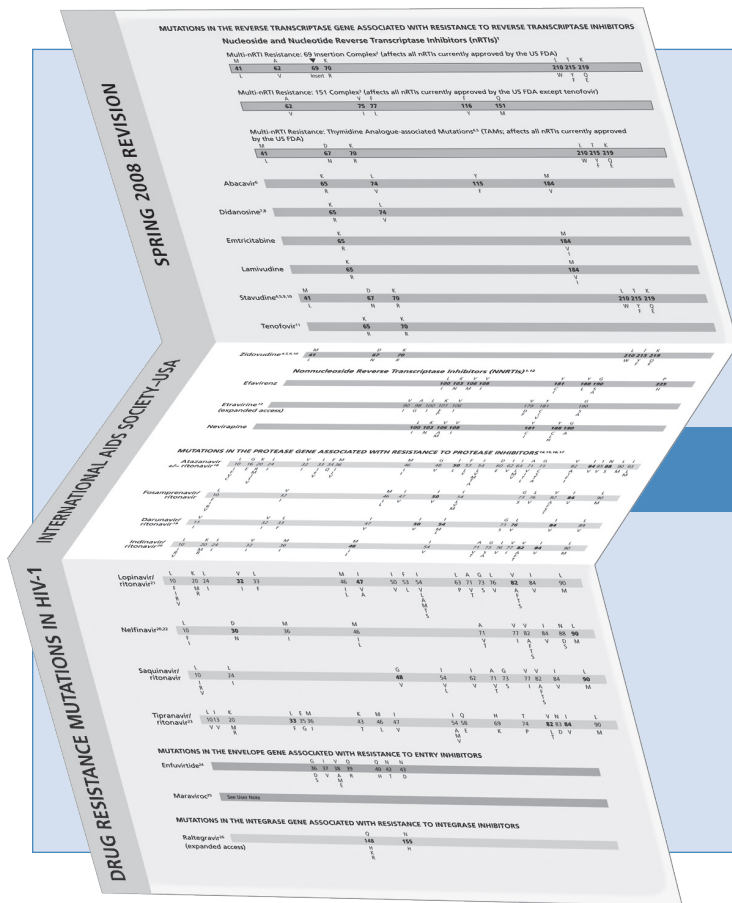
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Perspective

Insulin Resistance in HIV Infection: Drugs, Host Responses, or Restoration to Health?

Protease inhibitors (PIs) are widely assumed to be associated with a syndrome of insulin resistance accompanied by hyperlipidemia and fat redistribution. Insulin resistance in HIV infection has numerous other causes, however, which include not only the direct effects of antiretroviral drugs but also factors such as aging and restoration to health accompanied by fat accumulation. Studies of PIs in HIV-infected and noninfected patients indicate that some of these drugs are associated with reduced insulin sensitivity (greater acute versus chronic effects) that may be due to direct blockade of the insulin-sensitive glucose transporter in muscle and fat cells. Other studies have shown that insulin levels increase over time with antiretroviral therapy, likely the result of improved health, fat accumulation, and aging, and that increases in visceral fat and upper trunk fat are associated with a higher risk of insulin resistance in HIV-infected and -uninfected individuals alike. This article summarizes a presentation on insulin resistance in HIV infection made by Carl Grunfeld, MD, PhD, at the 10th Annual Ryan White HIV/AIDS Program Clinical Update in Phoenix in June 2007. The original presentation is available as a Webcast at www.iasusa.org.

Protease inhibitors (PIs) are widely assumed to induce a syndrome of insulin resistance accompanied by hyperlipidemia and fat redistribution that resembles the metabolic syndrome with its increased risk of cardiovascular disease. Researchers now believe, however, that numerous factors contribute to the metabolic alterations observed in HIV-infected patients and that some of these factors may be overlooked if only a single cause is assumed.

Insulin Resistance

Insulin resistance exists, but it cannot be diagnosed accurately in the clinic. Clinical insulin assays are, in short, terrible for providing absolute measurements of insulin; these assays were developed as a clinical tool to detect inappropriate insulin levels during hypoglycemia by assessing whether insulin levels change during fasting. (Research insulin assays may work better.) Many studies assess insulin resistance using a homeostasis model assessment of insulin resistance

(HOMA-IR), which is calculated as follows: insulin concentration ($\mu\text{U/mL}$) multiplied by the result of glucose concentration (mmol/L) divided by 22.5; a score of higher than 4 indicates insulin resistance, which is useful in epidemiologic studies. Note, however, that the calculation depends on measuring insulin level and therefore does not work using clinical laboratory measurements. Similar calculations can be derived from results of glucose tolerance testing. The current gold standards are the insulin tolerance test and the euglycemic-insulin clamp technique, the latter of which measures insulin-mediated glucose disposal (glucose infusion rate divided by insulin level, or M/I). Neither is appropriate for use in the clinic. The bottom line is that insulin resistance is inferred rather than accurately measured in a given patient.

A diagnosis of insulin resistance portends an unfavorable outcome. Insulin resistance is the first step toward diabetes, but it must be accompanied by a (largely genetically determined) reduction in insulin secretion. Insulin resistance is one of the World Health Organization (WHO) criteria for metabolic syndrome, but the WHO criteria

are rarely used because of the need to perform insulin clamp studies to make the diagnosis (Kahn et al, *Diabetes Care*, 2005). Epidemiologically, insulin resistance is strongly linked with coronary artery disease, and debate exists over whether it is the prime causal factor or a risk marker. Factors known to cause insulin resistance outside the setting of HIV infection include obesity, especially visceral obesity; physical inactivity; the use of some drugs (eg, glucocorticoids and niacin); and acute bacterial infection. Keep in mind, however, that approximately 20% of healthy, thin individuals have insulin resistance.

Insulin Resistance in HIV Infection: Effects of Protease Inhibitors

Studies of acute HIV infection usually show insulin resistance and hyperglycemia (with hypoglycemia appearing during sepsis). Early studies of the insulin profile in HIV infection (Hommes et al, *Metabolism*, 1991) were remarkable in that no insulin resistance or hyperglycemia was observed; in fact, patients were often thin, and clamp studies indicated increased insulin sensitivity. In 2000, Mulligan and colleagues reported findings in a study that assessed changes in glucose and insulin before and approximately 3 months after the addition of a PI (indinavir, saquinavir, or ritonavir) or lamivudine to stable antiretroviral therapy and compared those results to those in patients maintained on a stable regimen that did not include a PI or lamivudine (control). As shown in Figure 1, patients receiving a PI had a clinically trivial but nonetheless remarkable increase in glucose concentrations over the short study period, as well as a doubling in insulin concentrations; also, no change in body fat distribution (limb fat and trunk fat) was evident (Mulligan et al, *JAIDS*, 2000). These findings indicate that

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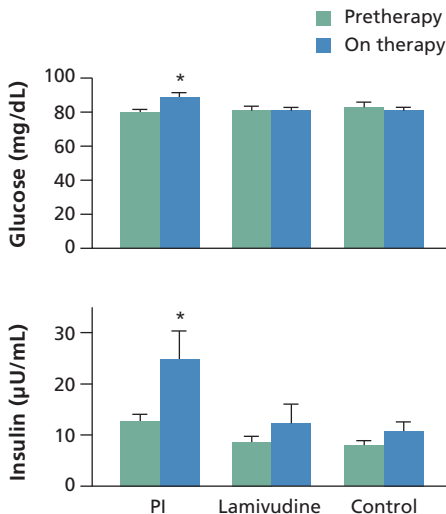


Figure 1. Changes in plasma glucose and insulin levels in HIV-infected patients after adding a protease inhibitor (PI) (indinavir, n = 16; saquinavir, n = 2; or ritonavir, n = 2) or lamivudine (n = 9) to stable treatment containing neither (control, n = 12). Asterisks indicate statistically significant difference. Adapted from Mulligan et al, *JAIDS*, 2000.

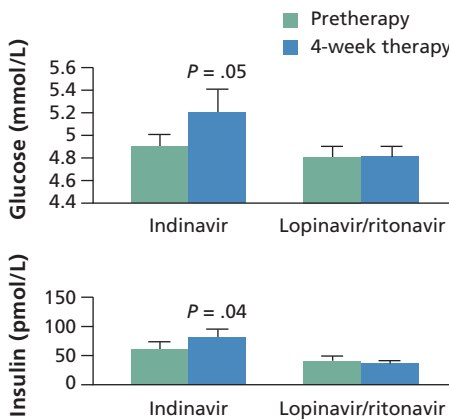


Figure 2. Plasma glucose and insulin levels before and after 4 weeks of protease inhibitor treatment in healthy HIV-seronegative patients. Adapted from Noor et al, *AIDS*, 2001, and Lee et al, *AIDS*, 2004.

whereas PIs do cause some metabolic changes, the changes are not mediated by alteration of body composition.

Dr Grunfeld and colleagues thus performed studies in which indinavir or lopinavir/ritonavir were administered to healthy HIV-seronegative patients to determine whether the metabolic effects in HIV-infected patients might be

related to restoration of health or a direct result of the PI. These studies again showed no alteration in visceral or subcutaneous fat with PI administration. Indinavir, but not lopinavir/ritonavir, was associated with statistically significant increases in fasting glucose and insulin concentrations (Figure 2; Noor et al, *AIDS*, 2001; Lee et al, *AIDS*, 2004).

These findings thus suggest that the effects of at least some PIs on metabolism do not depend on antiretroviral therapy–related restoration of health and improved immune response or on changes in body composition. This is not to say, however, that metabolic changes related to body composition factors do not also occur. Clamp studies in the patients receiving indinavir showed a statistically significant decrease in insulin sensitivity; results of 2-hour oral glucose tolerance testing showed a statistically significant increase in glucose levels, with 1 patient meeting the criterion for diabetes and 2 patients meeting the criterion for impaired glucose tolerance (Figure 3). However, the insulin resistance observed in these patients was not classic insulin resistance because no resistance to the effects of insulin on lipid metabolism was observed. Measurement of free fatty acid levels during oral glucose tolerance testing showed that levels were normally suppressed in both indinavir and lopinavir/ritonavir recipients (Figure 4); similar findings were made in clamp studies.

The findings indicating normal lipid kinetics in these subjects are of particular interest given in vitro findings indicating that PIs bind to and block the insulin-sensitive glucose transporter (GLUT4; Hruz, *Am J Infect Dis*, 2006). Protease inhibitors decreased insulin-stimulated glucose transport in fat cells with no blockade of any aspect of insulin activation (eg, phosphorylation, lipid metabolism). The direct effect on GLUT4 was supported by showing that glucose transport was blocked in non-insulin-sensitive cells transfected with GLUT4. These effects of PIs were evident within minutes of exposure.

Dr Grunfeld and colleagues therefore examined the effects of single doses of PIs in healthy HIV-seronegative patients. As shown in Figure 5, every patient ex-

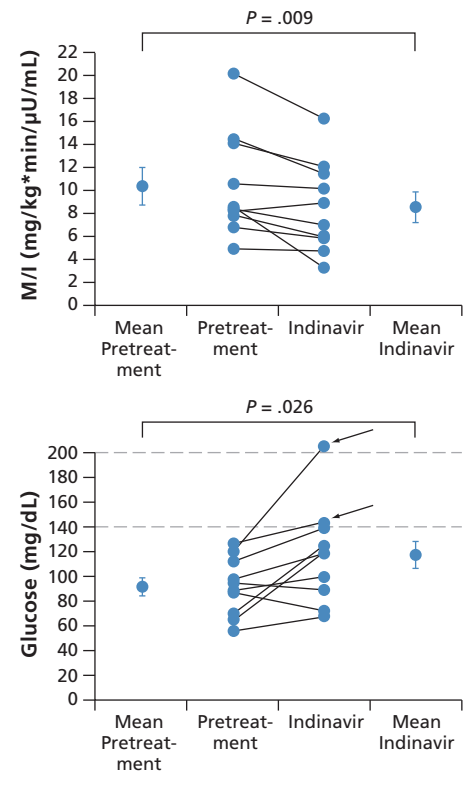


Figure 3. Changes in insulin-mediated glucose disposal (glucose infusion rate divided by insulin level [M/I]) in clamp studies (top), and glucose levels in 2-hour oral glucose tolerance testing (bottom) in HIV-seronegative patients receiving 4 weeks of indinavir. Top dashed line indicates diabetes threshold; bottom dashed line, impaired glucose tolerance threshold. Adapted from Noor et al, *AIDS*, 2001.

hibited insulin resistance (reduced M/I), with the reduction in glucose infusion rate during the clamp study evident within 30 minutes. Glucose disposal during the hyperinsulinemic clamp is caused by insulin increasing glucose transport by increasing the activity of GLUT4 in muscle and fat. Studies of other PIs showed that single-dose ritonavir—but not amprenavir—reduced M/I (Figure 6), and that 10 days of lopinavir/ritonavir also reduced M/I. The picture that has emerged from these studies is that the effects caused by some PIs of increasing insulin resistance are strong in the short term and reduced with long-term dosing (Lee et al, *Curr HIV/AIDS Rep*, 2000). The greatest effects are observed with indinavir and full-dose ritonavir, the drugs in use when diabetes began to appear in HIV-infected patients.

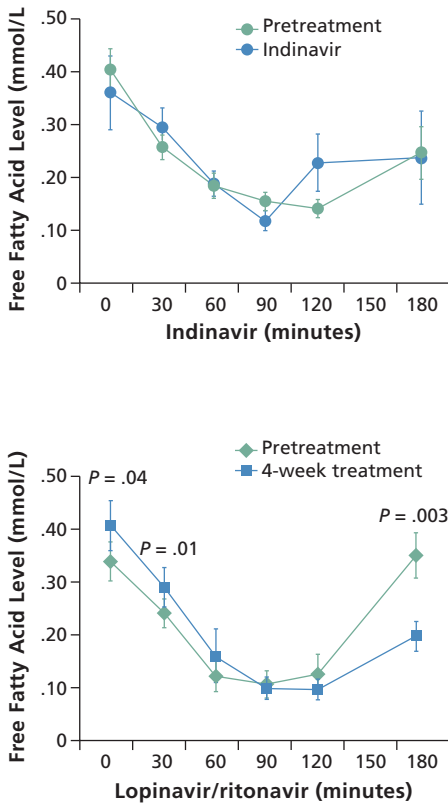


Figure 4. Comparison of free fatty acid levels during oral glucose tolerance testing in healthy HIV-seronegative patients receiving 4 weeks of indinavir or lopinavir/ritonavir. Adapted from Noor et al, *AIDS*, 2001, and Lee et al, *AIDS*, 2004.

Other Factors in Insulin Resistance: Restoration of Health, Fat, and Aging

The effects of indinavir on insulin resistance are greater in HIV-infected patients than in noninfected patients, indicating that factors in addition to the potential blocking of insulin-mediated glucose transport are operative in HIV infection. That such factors are active in addition to the specific drug effect of some PIs is supported by long-term data. In the Flexible Initial Retrovirus Suppressive Therapies (FIRST) study, patients in whom a PI was added to treatment had an early increase in insulin levels compared with those adding a nonnucleoside analogue reverse transcriptase inhibitor (NNRTI) or PI plus NNRTI treatment; however, follow-up of more than 5 years showed

that all groups had a statistically significant increase in insulin levels over time (Figure 7). Shorter-term follow-up among nonrandomized patients receiving didanosine/stavudine versus abacavir/lamivudine showed a statistically nonsignificant greater increase in the patients receiving nucleoside analogue reverse transcriptase inhibitors (nRTIs) than in patients receiving NNRTIs (nRTIs are themselves associated with specific effects on metabolism that are not discussed here; Shlay et al, *JAIDS*, 2005; Shlay et al, *JAIDS*, 2007).

The factors causing increased insulin resistance in these treated patients, which appear to overwhelm the changes produced by PIs, are likely related to changes such as improved health and gaining of body fat, as well as aging. In the Fat Redistribution and Metabolism (FRAM) study (Grunfeld et al, *JAIDS*, 2007), Dr Grunfeld and colleagues assessed metabolic and body composition profiles in nondiabetic HIV-infected patients and healthy controls. Glucose levels were similar in male and female patients and controls; HOMA-IR levels were somewhat higher in HIV-infected women, but not in HIV-infected men, compared with controls. Multivariate analysis showed that being in the upper tertiles for visceral fat and upper trunk fat was associated with a markedly increased risk of having a HOMA-IR value higher than 4 (Table 1). The relationship between fat deposits and insulin resistance as

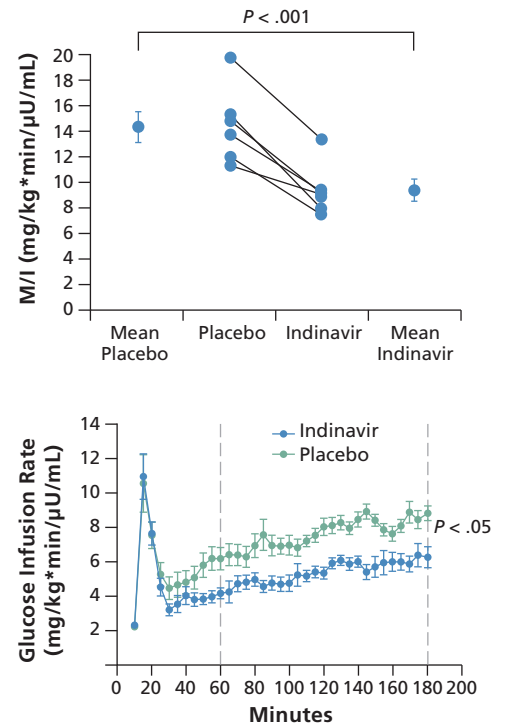


Figure 5. Effect of single dose of indinavir in HIV-seronegative patients on insulin sensitivity (M/I; top) and on glucose infusion rate over time during clamp study (bottom).

assessed by HOMA-IR values above 4 is stronger in controls than in HIV-infected subjects because other factors, such as antiretroviral drugs, contribute to insulin resistance in patients with HIV infection that are not operative in controls. Factors predictive of greater visceral fat were male sex, white race, increasing age, not smoking, and reduced physical activity (Table 2).

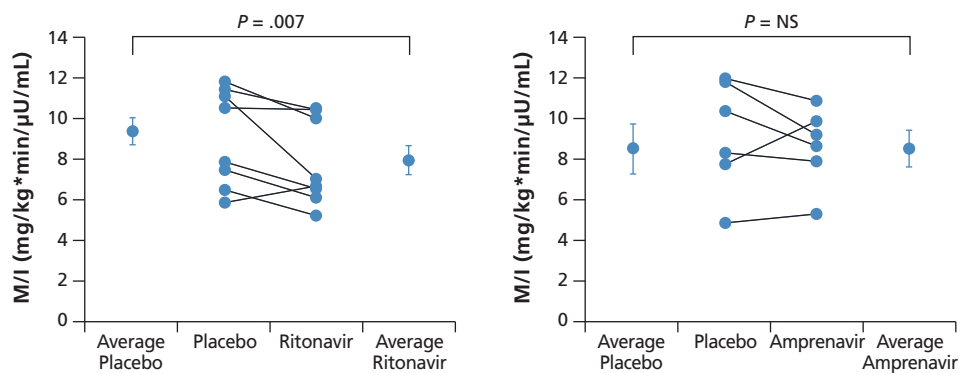


Figure 6. Effect of single doses of ritonavir (left) and amprenavir (right) on insulin sensitivity (M/I) in HIV-seronegative patients. NS indicates not statistically significant.

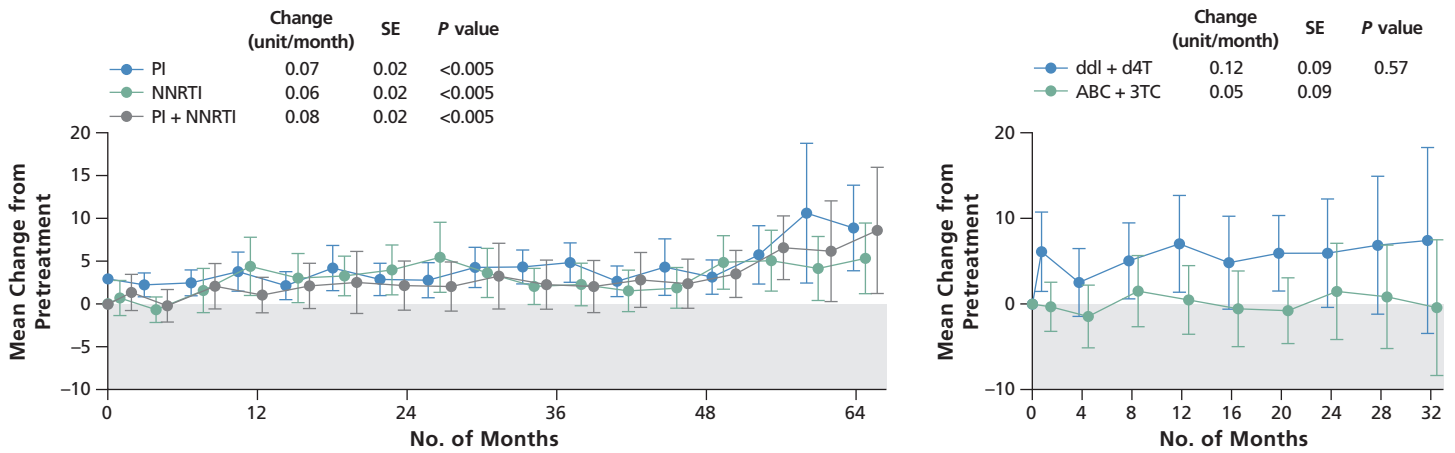


Figure 7. Changes in insulin concentration in patients receiving protease inhibitor (PI), nonnucleoside analogue reverse transcriptase inhibitor (NNRTI), or PI plus NNRTI treatment (left) or didanosine (ddl) plus stavudine (d4T) versus abacavir (ABC) plus lamivudine (3TC) treatment (right) in the Flexible Initial Retrovirus Suppressive Therapies (FIRST) study. SE indicates standard error. Adapted from Shlay et al, *JAIDS*, 2005, and Shlay et al, *JAIDS*, 2007.

Table 1. Effect of Tertile of Visceral Adipose Tissue and Upper Trunk Fat on Risk for Insulin Resistance (HOMA-IR > 4) in Healthy Control and HIV-infected Patients in Fat Redistribution and Metabolism Study^a

	Controls		HIV-infected Patients	
	Odds Ratio	P Value	Odds Ratio	P Value
Visceral Adipose Tissue				
3rd vs 1st tertile ^b	12.1	.0002	3.2	<.0001
2nd vs 1st tertile ^b	1.9	.31	1.9	.002
Upper Trunk Fat				
3rd vs 1st tertile ^b	9.0	.001	2.1	.001
2nd vs 1st tertile ^b	2.4	.20	1.2	.33

HOMA-IR indicates homeostasis model assessment of insulin resistance.

^aThe model controls for ethnicity, age, sex, alcohol use (HIV group only), current “crack” and other cocaine use (HIV group only), physical activity (control group only), and adequacy of food (control group only).

^bTertiles of control group are used as reference to directly compare HIV group with control group.

Should Insulin Resistance Be Treated?

Insulin resistance in HIV-infected patients is treatable with lifestyle modification or drug therapy. The “prediabetic” use of antidiabetic drugs is not currently approved by the US Food and Drug Administration. Small studies of metformin and rosiglitazone in HIV-infected patients with insulin resistance have shown statistically significant decreases in insulin area-under-the-curve

concentration with both drugs (Hadi-gan et al, *JAMA*, 2000, and Hadigan et al, *Ann Intern Med*, 2004). The Diabetes Prevention Program study in individuals from the general population with impaired fasting glucose or impaired glucose tolerance showed that a rigorous lifestyle intervention (diet and exercise) was associated with a 68% reduction in incidence of diabetes compared with a 31% reduction with metformin treatment; the thiazolidinedione troglitazone was discontinued from this study (and removed from the market

after reports of severe and fatal hepatotoxicity) but was associated with reductions in incidence of diabetes at early time points in the study.

Other data also indicate the benefit of thiazolidinedione treatment in “preventing” diabetes in individuals with impaired fasting glucose and impaired glucose tolerance. However, an increased risk of myocardial infarction and of bone fracture in women has been reported with rosiglitazone treatment, and both rosiglitazone and pioglitazone (the 2 thiazolidinediones currently on the market) have been associated with lower bone mineral density. Whether treatment of insulin resistance before development of diabetes is associated with long-term benefits has yet to be determined.

Conclusions

The development of insulin resistance in HIV-infected patients is multifactorial, with causes including restoration to health, direct drug effects of PIs and nRTIs, increased visceral adipose tissue, age, and inactivity. Insulin resistance is hard to diagnose accurately but can be inferred. Treatment of insulin resistance is similar in HIV-infected patients and uninfected individuals, but the long-term value of initiating treatment before the development of diabetes is unknown.

Table 2. Effects of Subject Characteristics on Visceral Adipose Tissue in Fat Redistribution and Metabolism Study

	Men		Women	
	Percent Effect	P Value	Percent Effect	P Value
Ethnicity, vs White				
African American	-55	.001	-21	.089
Hispanic	-3	.74	+6	.78
Age, per decade	+31	<.0001	+18	.031
Current Smoker	-19	.003	-32	<.0001
Physical Activity, vs 1st Quartile (least)				
2nd quartile	-12	.24	+2	.79
3rd quartile	+1	.82	-12	.57
4th quartile	-20	.020	-21	.32

Presented by Dr Grunfeld in June 2007. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Grunfeld in May 2008.

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Perspective

HIV-Associated Neurocognitive Disease Continues in the Antiretroviral Era

Despite the ability to suppress viral replication with antiretroviral therapy, HIV-associated neurocognitive disturbances can still be detected in nearly half of patients. Neurologic dysfunction before initiating or in the absence of antiretroviral treatment is primarily the result of neuronal dysfunction or loss from direct viral effects, whereas that in patients receiving antiretroviral therapy appears to be associated at least in part with inflammation driven by chronic low-level infection. Contributing factors may include genetic differences in HIV and human hosts and aging of patients. This article summarizes a presentation on HIV-associated neurocognitive disorder made by David B. Clifford, MD, at an International AIDS Society–USA Continuing Medical Education course in New York in October 2007. The original presentation is available as a Webcast at www.iasusa.org.

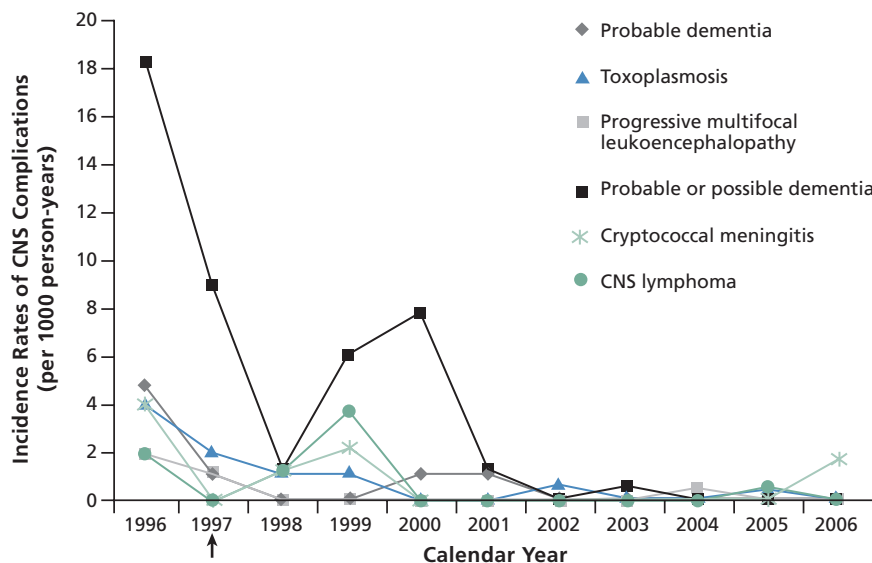


Figure 1. Rates of central nervous system (CNS) complications in HIV infection since the advent of potent antiretroviral therapy (arrow). N. Sacktor, MD, written communication, 2007.

The rates of reported HIV-associated central nervous system (CNS) complications have declined since the advent of potent antiretroviral therapy (Figure 1). Although our progress is impressive, a close look shows that HIV-associated neurocognitive disturbance is still an important

issue despite the vast clinical improvements achieved with antiretroviral treatment. Systematic evaluation of more than 1000 clinic patients in the CNS HIV Antiretroviral Effects Research (CHAR-TER) cohort shows that neurologic impairment is present in 50% or more, a rate comparable to that in the pre-antiretroviral era (Figure 2). Many factors likely contribute to ongoing neurologic complications despite the ability of current drugs to profoundly suppress viral replication. These factors include ongo-

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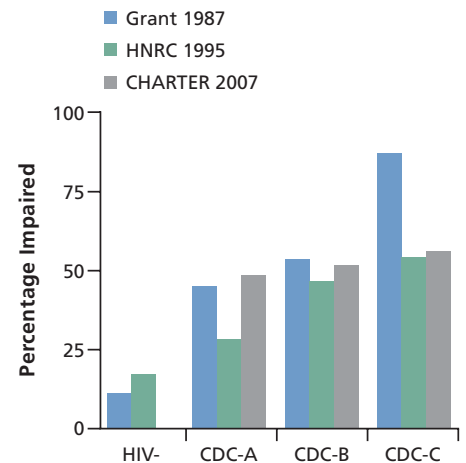


Figure 2. Percentages of subjects with HIV-associated neurocognitive disturbance before (Grant and HNRC) and after (CHARTER) the advent of potent antiretroviral therapy according to US Centers for Disease Control and Prevention category (CDC-A, -B, and -C) for HIV disease. HIV- indicates rates of neurocognitive disturbance in cohort subjects without HIV infection; HNRC, HIV Neurobehavioral Research Center; CHARTER, Central Nervous System HIV Antiretroviral Effects Research. Adapted from data courtesy of I. Grant, MD, for the HNRC and CHARTER groups.

ing viral replication and immune activation in the CNS, comorbid factors like the use of both nonprescription and prescription drugs, perhaps including antiretroviral drugs, coinfections like with hepatitis B and C, and genetic influences of both the virus and the host.

Neuronal Loss and Astrocyte Activation and Inflammation

Cross-sectional studies in the pre-potent antiretroviral era showed a correlation between cerebrospinal fluid (CSF) viral load and degree of cognitive impairment (Brew et al, *J Infect Dis*, 1997; Ellis et al, *Ann Neurol*, 1997; McArthur et al, *Ann Neurol*, 1997; Letendre et al,

Ann Neurol, 2004). More recent data have shown that virologic suppression in the CSF with antiretroviral treatment is associated with significant improvement in function. However, patients on antiretroviral treatment with suppression of HIV RNA levels in the CSF to 400 copies/mL or below can still develop HIV cognitive impairment (Clifford et al, *Neurology*, 2002), suggesting that ongoing damage resulting from immune

Table 1. Cerebrospinal Fluid Penetration of Established or Discontinued Antiretroviral Drugs

	CSF: Plasma Ratio
nRTIs	
Abacavir	0.3-0.42
Didanosine	0.16-0.19
Emtricitabine	0.04
Lamivudine	0.11
Stavudine	0.16-0.97
Tenofovir	<0.05
Zalcitabine*	0.09-0.37
Zidovudine	0.3-1.35
Fusion Inhibitor	
Enfuvirtide	NA
NNRTIs	
Delavirdine	0.02
Efavirenz	0.01
Nevirapine	0.28-0.45
PIs	
Amprenavir*	<0.05
Atazanavir	0.0021-0.0226
Fosamprenavir	<0.05
Indinavir	0.02-0.76
Lopinavir	<0.05
Nelfinavir	<0.05
Ritonavir	<0.05
Saquinavir	<0.05

CSF indicates cerebrospinal fluid; nRTI, nucleoside (or nucleotide) analogue reverse transcriptase inhibitor; NA, not available; NNRTI, nonnucleoside analogue reverse transcriptase inhibitor; PI, protease inhibitor. Asterisk indicates no longer on the market. Adapted from Simpson, *Clin Care Options, HIV*, 2008.

activation driven by chronic low-level infection may account for continued neurologic complications in the potent antiretroviral era.

Many antiretroviral agents exhibit poor CSF and brain penetration (Tables 1, 2). Some of the older drugs have better CNS penetration, and many agents included in the more potent newer regimens penetrate poorly. CCR5 antagonists are an exception among the newer agents, although use of these agents in patients with HIV dementia is likely to be limited by the fact that such patients typically have more advanced disease and are thus more likely to have dual- or mixed-tropic virus that is insensitive to CCR5 antagonism. Through work with the CHARTER cohort, Letendre and colleagues have developed a CNS penetration effectiveness (CPE) scoring system for antiretroviral drugs (Table 3). Many drugs used in patients who have experienced multiple drug failures are in the poorest penetration group (score 0), and some of those with the best penetration (score 1) are no longer widely used. A study of CHARTER cohort patients with plasma HIV RNA levels of less than 50 copies/mL was performed using an ultrasensitive assay capable of detecting virus in CSF to the level of 2.5 copies/mL. Patients with CSF viral loads below the assay detection limit were receiving antiretroviral therapy with a CPE score of 2.0 (eg, 2 drugs from Table 3 with scores of 1), whereas patients with HIV RNA levels of 2.5 to 50 copies/mL were receiving treatment with a CPE score of 1.25 ($P = .005$) (Letendre, CROI, 2007). Thus, low-level viral replication is likely to be occurring in many patients with apparent suppression on antiretroviral therapy and may account for ongoing neurologic damage.

After entry into the CNS via monocytes, HIV could impair or kill neurons by viral replication or by toxic effects of HIV gp120 and Tat proteins on these cells. Although current antiretroviral drugs can inhibit viral replication to low levels, low-level replication may still cause dysfunction of nerve cells via ongoing inflammatory response and astrocytic gliosis, mediated, for example, by tumor necrosis factor α and monocyte chemoattractant protein 1 (MCP-1). This protein is

Table 2. Cerebrospinal Fluid Penetration of Newer and Investigational Antiretroviral Drugs

	Estimated Penetration
nRTIs	
Dexelvucitabine (D-d4FC)*	Intermediate
SPD754*	Intermediate
Fusion/Entry Inhibitors	
Maraviroc	Intermediate to higher
Vicriviroc*	Higher
NNRTIs	
Capravirine*	Lower
Etravirine	Lower
PIs	
Darunavir	Intermediate to higher
Tipranavir	Lower

nRTI indicates nucleoside analogue reverse transcriptase inhibitor; NNRTI, nonnucleoside analogue reverse transcriptase inhibitor; PI, protease inhibitor. Asterisk indicates investigational drug. Based on evaluation of S. Letendre, MD.

potent in attracting inflammatory cells into infected organs and has high levels of expression in the brain. In a study by Chang and colleagues (Chang et al, *Antivir Ther*, 2004), CSF MCP-1 levels were higher than serum MCP-1 levels at baseline in antiretroviral drug-naive, HIV-infected individuals (Table 4); initiation of antiretroviral treatment resulted in reduction of CSF viral load but not to undetectable levels, and MCP-1 levels were reduced in both serum and CSF but remained relatively elevated in CSF. Using particular metabolites detected by magnetic resonance spectroscopy to characterize neuronal damage versus the glial activation and inflammatory component of cell dysfunction (a technique termed principal component analysis), these investigators found a statistically significant inverse relationship ($r = -0.59$; $P = .0008$) between neuronal damage (neuronal component) and MCP-1 level in the brain before treatment and no such relationship after treatment. They also found a statistically significant positive correlation ($r = 0.70$; $P = .0002$) between MCP-

Table 3. Antiretroviral Central Nervous System Penetration Effectiveness Scores Derived from the CHARTER Cohort

	Increasing CNS Penetration →		
	0	0.5	1
nRTIs	Didanosine Tenofovir Zalcitabine*	Emtricitabine Lamivudine Stavudine	Abacavir Zidovudine
NNRTIs		Efavirenz	Delavirdine Nevirapine
PIs	Nelfinavir Ritonavir Saquinavir Saquinavir/r Tipranavir/r	Amprenavir* Atazanavir Atazanavir/r Fosamprenavir Indinavir	Amprenavir*/r Fosamprenavir/r Indinavir/r Lopinavir/r
Other	Enfuvirtide		

CHARTER indicates Central Nervous System HIV Antiretroviral Effects Research; CNS, central nervous system; nRTI, nucleoside analogue reverse transcriptase inhibitor; NNRTI, nonnucleoside analogue reverse transcriptase inhibitor; PI, protease inhibitor; r, ritonavir. Asterisk indicates no longer on the market. Adapted from Letendre et al, *CROI*, 2006.

1 level and glial activation (glial component) after antiretroviral treatment, with no correlation before treatment. Findings like these support a scenario in which neurologic dysfunction before initiating or in the absence of antiretroviral treatment is predominantly associated with neuronal loss caused by direct viral mechanisms, whereas such dysfunction in patients on antiretroviral therapy is associated with chronic cellular activation and consequent dysfunction of nerve cells (Figure 3).

Virus and Host Genetic Factors

Areas of the world in which the HIV clade C variant is predominant (eg, parts of Africa), appear to have a lower frequency of HIV-related neurotoxicity than do areas where clade B infection predominates (eg, the United States). Recent studies indicate that the Tat protein in clade C virus may be less directly toxic to neural cells than that in clade B virus and is associated with reduced production of MCP-1 from astrocytes (Mishra et al, *Ann Neurol*, 2008).

Some evidence also suggests that human genetic variation is associated with a predisposition to neurologic complications. For example, 1 study showed that patients with a specific MCP-1 genotype had a 4.5-fold in-

crease in risk of HIV-associated dementia; the genotype was associated with increased transcriptional activity for MCP-1 and greater tissue infiltration of monocytes (Gonzalez et al, *Proc Natl Acad Sci USA*, 2002).

Aging and Amyloid

With antiretroviral therapy, patients are living longer, and increasing age has consistently been a risk factor for development of HIV-associated cognitive impairment. This observation has led to consideration of the possible relationship between HIV-associated dementia and dementia of Alzheimer type (DAT).

Recent investigations have shown that β -amyloid deposition, which accounts for DAT senile plaques, can be identified in approximately half of HIV-seropositive patients' brains, both in plaques and in intraneuronal locations (Green et al, *AIDS*, 2005). The β -amyloid deposition is likely multifactorial. A chronic inflammatory state may create an environment conducive to augmented amyloid-associated toxicity. Antiretroviral treatment may predispose the patient to amyloid deposition, both by facilitating aging and by causing metabolic toxicity and ubiquitin-proteasome dysfunction. Tat protein toxicity may also be associated with amyloid deposition. This concept is supported by the results of an in vitro study, which showed that Tat markedly inhibits neprilysin, a neuronal endopeptidase that degrades β -amyloid (approximately 80% or greater inhibition at Tat concentrations of 10-100 ng/mL; Rempel and Pulliam, *AIDS*, 2005).

In normal metabolism, amyloid is constantly turned over in the brain and leaches into the CSF. When concentrations in the brain are elevated, the amyloid aggregates into plaques. In DAT patients, high levels of brain amyloid (measured as Pittsburgh compound B binding) are correlated with low levels of β 42-amyloid in the CSF (regardless of clinical status), and normal controls have higher CSF amyloid levels (Fagan, *Ann Neurol*, 2006; Fagan et al, *Arch Neurol*, 2007). In a study of 50 non-HIV-infected controls (clinical dementia rating [CDR] = 0), 71 subjects with DAT

Table 4. Effect of Antiretroviral Treatment on Viral Load and Monocyte Chemotactic Protein 1 Level

	Antiretroviral Therapy– Naive Subjects with Follow-up (n = 31)	3 Months after Antiretroviral Treatment (n = 31)
CD4+ count (cells/ μ L)	183 (26) ^a	310 (34), $P < .0001$
Plasma HIV RNA level (copies/mL)	187,727 (49,527)	1163 (629), $P = .0004$
CSF HIV RNA level (copies/mL)	7500 (1626)	235 (134), $P = .0002$
Serum MCP-1 level (pg/mL)	541 (102)	285 (47), $P = .005$
CSF MCP-1 level (pg/mL)	637 (81)	410 (36), $P = .009$

^aData are mean (standard error). CSF indicates cerebrospinal fluid; MCP-1, monocyte chemotactic protein 1. Adapted from Chang et al, *Antivir Ther*, 2004.

(CDR = 0.5/1), and 40 HIV-infected subjects (29 with minor cognitive motor disorder, 11 with HIV-associated dementia), Dr Clifford's group found that CSF β 42-amyloid levels in patients with HIV-associated neurocognitive disorder were similar to those in DAT subjects and statistically significantly lower than those of controls (Figure 4). Tau protein CSF levels, which are also elevated in DAT, were not elevated in HIV-infected subjects, showing that the condition present in the HIV-associated disorder is not the same as DAT but nevertheless appears to involve amyloid metabolism.

What Should Be Done?

As HIV practitioners, we must be aware of possible ongoing disruption of neurocognitive function in our patients who otherwise appear to be doing well and to the potential for HIV-related

neurologic damage in the HIV-infected population as a whole. Optimization of HIV therapy in this regard may include starting antiretroviral treatment early enough to avoid neuronal loss and using viral control in the CNS as an efficacy measure. Good CNS penetration does not appear to have been a goal of recent antiretroviral drug development, and we need to support efforts to decide if brain penetration is a crucial component in the design of therapy. We should also encourage further research to develop effective means to protect the brain from alternate pathways of damage. New therapies for amyloid toxicity are being developed, and these may eventually play a role in the treatment of HIV-associated dementia. A current AIDS Clinical Trials Group (ACTG) study (A5235) is assessing the effects of minocycline (a tetracycline-class antibiotic) in patients with HIV-related cognitive impairment. This

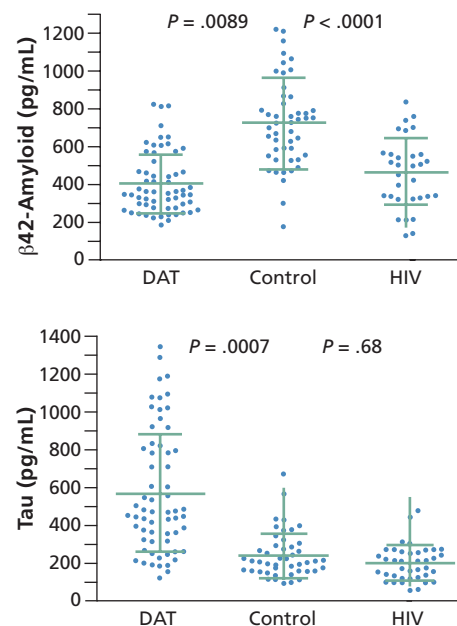


Figure 4. Cerebrospinal fluid (CSF) β 42-amyloid (top) and Tau protein (bottom) levels in dementia of Alzheimer type (DAT) subjects, non-HIV-infected controls, and patients with HIV-associated neurocognitive disorder. Adapted from Clifford et al, IAC, 2007.

drug has been shown to protect against encephalitis in the simian immunodeficiency virus model in association with dramatically reduced MCP-1 levels; potential beneficial effects include an anti-inflammatory and neuroprotective effect via suppression of p38 mitogen-activated protein kinase, antioxidant and antiapoptotic effects, inhibition of matrix metalloproteinases that may damage the blood-brain barrier, as well as a possible antiviral effect.

Presented by Dr Clifford in October 2007. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Clifford in May 2008.

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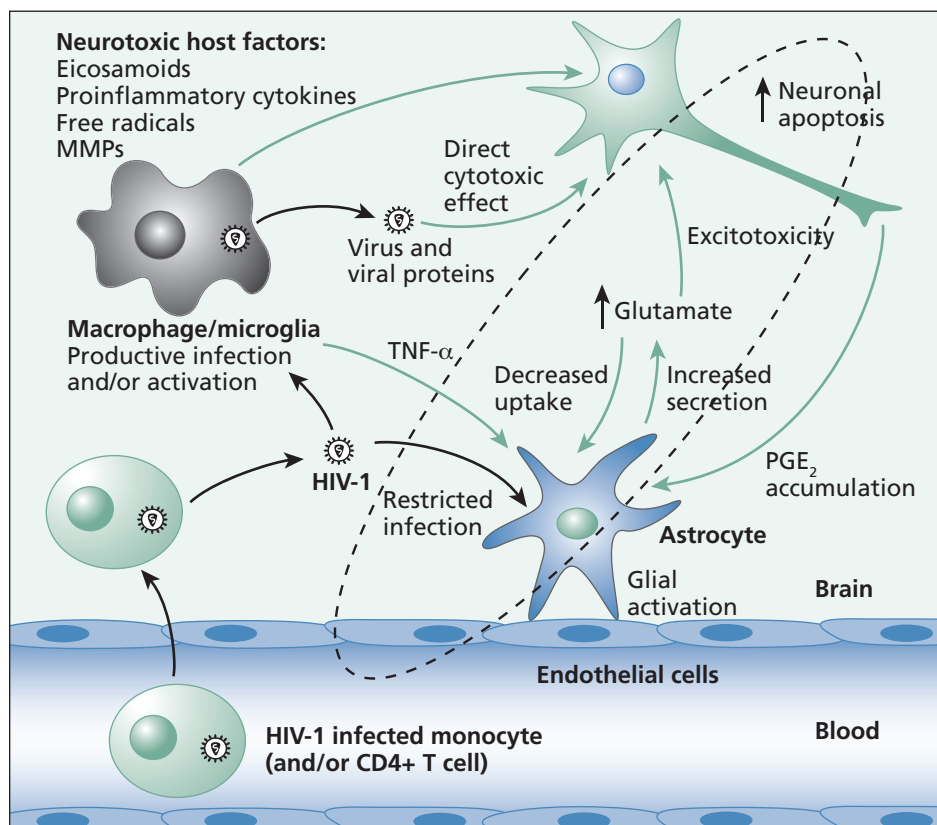


Figure 3. HIV neuropathogenesis. Circled area indicates inflammatory factor-driven neurotoxicity that appears to account for ongoing dysfunction during antiretroviral therapy. MMP indicates matrix metalloproteinases; TNF- α , tumor necrosis factor α ; PGE₂, prostaglandin 2. Adapted from Jones and Power, *Neurobiol Dis*, 2006.

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Commentary

Impact of Psychiatric Disorders on the HIV Epidemic

Mental illness continues to fuel the HIV epidemic. There is a high prevalence of mental disorders in the HIV-infected population and a high prevalence of HIV infection in the mentally ill. Without effective treatment of mental disorders, HIV treatment outcome is poor, and transmission of disease continues. High frequencies of mental illness are found in corrections facilities, among the homeless, among injection drug users, and in patients attending sexually transmitted disease clinics. Such populations must be targeted for effective mental health treatment if overall outcomes of HIV treatment are to be improved and transmission of HIV is to be reduced. This article summarizes a presentation on mental illness and the HIV epidemic made by Andrew F. Angelino, MD, at the 10th Annual Ryan White HIV/AIDS Program Clinical Update in June 2007. The original presentation is available as a Webcast at www.iasusa.org.

Considerable overlap exists among the population of individuals with mental disorders and the HIV-infected, homeless, and corrections populations, with the high frequency of mental disorders in these latter populations associated both with risk behaviors for acquiring and transmitting infection and with poorer outcome as the result of failure to seek or adhere to appropriate treatment. Mental disorders thus play a major role in fueling the ongoing HIV epidemic, and treatment of these disorders would go a long way toward improving overall HIV care and reducing transmission. We know where many at-risk individuals are—whether in corrections facilities or neighborhoods marked by high rates of injection drug use (IDU)—and we need to convince our legislators and other public servants that extending effective treatments to these populations benefits society as a whole.

Mental Disorders in HIV-infected Persons

There is a clear interrelationship of HIV infection and mental illness. In the Johns Hopkins Moore (HIV) Clinic, the

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prevalence of non-substance abuse axis I disorders in new medical intakes (ie, patients coming for their first visit after receiving a diagnosis of HIV infection) was measured at 54%, including major depression in 20% and adjustment disorder in 18%. Substance use disorders were found in 74% of patients, cognitive impairment in 18%, and personality disorder in 26%. The emotional response to the recent diagnosis is probably largely reflected in the rate of adjustment disorder, but the remainder of the disorders predate the diagnosis. Prevalence rates of HIV infection in mentally ill inpatient and outpatient populations have been reported at 5.2% to 22.9% (Carey, *Prof Psychol Res Pract*, 1995; Cournos, *Clin Psychol Res*, 1997; McKinnon, *Psychiatr Serv*, 1998), compared with a rate of 0.3% to 0.4% in the US general population over a comparable time period (McQuillan, *J Acquir Immune Defic Syndr Hum Retrovirol*, 1997).

Although some people acquire HIV infection via an isolated sharing of a contaminated needle or an unprotected sexual encounter, these are unusual episodes. Far more frequently, infection is acquired when risk behaviors are chronically repeated, and mental illness is a significant contributor to the repetition of risk behaviors, as well as to the likelihood of winding up in envi-

ronments in which risk behaviors are both more common and more likely to result in acquiring infection.

The effect of having significant mental illness on one's life outcomes—relationships, education, employment, socioeconomic status, etc—has been shown to be a “downward drift.” This means that more mentally ill people are living, often with few social and emotional supports, in impoverished areas where illicit drug use is rampant. In such areas, because the rates of IDU are high, exposure to drugs of abuse is also high, and therefore initial use becomes more likely. Early users are at high risk of sharing needles and the other “works” of drug use; the median time to getting one's own “outfit” in 1 study was 1.67 years (Waldorf D, *Criminal Justice Policy Rev*, 1989). In areas where IDU is prevalent, HIV infection is also prevalent, so needle-sharing in these areas tends to increase the risk of transmission. Determining who is in need of mental health care is not difficult, and we need to concentrate on such individuals and such areas if we are to make a serious inroad to stopping continued transmission and poor outcomes of HIV treatment.

Various studies have shown that outcomes of HIV treatment are worse in individuals with untreated mental illness. HIV-infected women with chronic depressive disorder have a 2-fold greater relative risk of death than do those without depression, with the relative risk greater than 4-fold in women with CD4+ counts below 200 cells/ μ L (Ickovics, *JAMA*, 2001). Patients with psychiatric disorders have a slower rate of virologic suppression and a faster rate of virologic failure than do counterparts without such disorders (Pence, *J Acquir Immune Defic Syndr Hum Retrovirol*, 2007), and lack of psychological resources has been associated with increased mortality in HIV-infected women (Ickovics, *AIDS*, 2006).

At-risk Populations: Corrections and the Homeless

Data from 2005 in the United States indicated that 56% of the approximately 1,255,500 state prison inmates, 45% of the 156,600 federal inmates, and 64% of the 747,500 local jail inmates had histories or symptoms of mental health problems (US Department of Justice Bureau of Justice Statistics, 2006). Although the United States incarcerates more people than any other nation, the association of mental illness with incarceration is not limited to this country. For example, among 189 prisoners examined in Melbourne, Australia, 23% had current mood disorders and 3% had psychotic disorders; overall, 82% had at least 1 lifetime mental disorder, 26% had at least 2 lifetime disorders, and 69% had at least 1 lifetime substance use disorder (Herrman, *Am J Psychiatry*, 1991).

Statistics such as these suggest that we lock up our mentally ill more than hospitalize them. What happens when they are incarcerated? In open forums, US corrections administrators and legislators usually report that there is no problem with sex or drugs in prisons. In the 1840s, however, Fyodor Dostoevsky was in a Siberian prison, and later wrote about how wealthier inmates would have money sent to them, which was used to pay poorer inmates to shine their boots or repair their clothing; the poorer inmates used the money to buy vodka. If vodka could be had in the middle of nowhere in 1840, it is a good bet that there is heroin available in, say, the Baltimore City Jail or another facility in 2008.

And there is. A recent study on injection drug use in US corrections facilities estimated that 81% of men and women users had been incarcerated at least once, with 31% using drugs while in prison and 15% (49% of those using drugs) using injection drugs in prison (Clarke, *Subst Abuse*, 2001). Male sex and a higher number of incarcerations were associated with IDU in prison. Again, the problem is not just in the United States. A study in Greece found that 56% of men incarcerated for drug offenses used drugs while in prison, with

35% using injection drugs and 18% injecting drugs daily (Malliori, *Addiction*, 1998); 39% of inmates who knew they were HCV seropositive shared needles anyway (compared with 33% who had unknown HCV serostatus or knew that they were HCV seronegative).

The same tendencies toward risk behaviors that lead to prison, including but not limited to drug use, also lead to higher rates of HIV infection. Data from 1999 show that the AIDS rates per 100,000 population were 31.4 for the US general population versus 198.5 for the population in US corrections facilities. People in prison often eventually get out—notwithstanding that approximately 70% eventually return. Reentering society carrying the burden and experience of having been a noncitizen and carrying the additional label of “ex-felon” limits choices in future life, a state that itself can be considered a mental illness, and a treatable one.

We do not treat it, however. A recent US study showed that the top 2 activities engaged in within 24 hours of release were having sexual relations and using drugs (Seal, *AIDS and Behavior*, 2003). Explanations for the need for sexual activity included “proving I’m a man” and “making up for lost time,” and the offering of sex partners to ex-felons from gangs as a reward for their silence is also common. Explanations for drug use included “could not get as much inside,” drugs being offered as a reward for silence, and drugs being used as part of sexual encounters (eg, “crack” cocaine use). Released prisoners reported low rates of condom use immediately after incarceration, with rates higher for individuals with steady partners.

As sad as it seems, continued incarceration is associated with better HIV outcome than release and reincarceration. In a recent study matching released and reincarcerated HIV-infected prisoners 1:2 with unreleased HIV-infected prisoners, there were statistically significantly fewer individuals with undetectable viral load in the reincarcerated group, with a mean change in plasma HIV RNA level of $+1.29 \log_{10}$ copies/mL in the reincarcerated group versus $-0.03 \log_{10}$ copies/mL in the incarcerated group (Stephenson, *Pub-*

lic Health Rep, 2005). When prisoners are released, they are more likely to not take their medicines, and not keep follow-up appointments, and thus their disease worsens.

Another repository for those with mental disorders is the street. The risk of being homeless is high for the mentally ill in the United States. Part of the problem in this regard was the development and use of medicines beginning in the 1960s that markedly reduce the symptoms of such chronic illnesses as schizophrenia; these treatments did not make patients more socially competent or functional enough to have and hold a job, for example, although they were deemed “well” enough or “controllable” enough to live safely in the community for the most part. As a result, the public psychiatry system and state hospital systems began closing down; currently, in Maryland, for example, we have approximately 10% of the psychiatric beds that we had 20 years ago. Where are the people who used to be hospitalized chronically in those beds? Most are not living in stable housing; many are homeless or functionally homeless. Homelessness, of course, increases demoralization and worsens mental illness. Major depression has been diagnosed in 35% of homeless individuals and substance use disorder in 53% (Schanzer, *Am J Public Health*, 2007). A 1998 study reported 12% HIV seroprevalence among homeless, substance-using, mentally ill individuals (Rahav, *Subt Use Misuse*, 1998).

What Can Be Done?

So, what do we do about this mess? Needle-exchange programs work. It is true that all the addicts themselves do not always show up with the needles in community-based programs; frequently, they opt to pay others with drugs to bring in 200 or 300 needles. This economy works in its way, for it gets clean needles into the system and allows us to make contact with the person who brings in the needles and keep offering treatment.

Prison needle-exchange programs have been tried in other countries that publicly admit the possibility of a drug-

use problem in that setting. Table 1 shows findings in 6 1- or 2-year studies in Switzerland, Germany, and Spain; no cases of blood-borne virus infections were observed in any of the inmates in the study. In the system used, a prisoner is given a dummy syringe upon admission to the facility; the dummy syringe can be inserted into a vending-type machine to receive a clean needle in return, and then used needles can be exchanged for clean ones. The cells have small medicine cabinets containing a cup in which the needle is to be kept, both to prevent guards from getting needlestick injuries when they search the cells and to let program personnel know that they should leave pamphlets offering treatment. Any drugs found are removed, because drug use is illegal and discouraged, and if the needle is found anywhere but in the cup, punitive measures are taken. So long as the needle is left in the cup, however, it is not removed. Inmates in some of these studies reported that they used less drugs simply because having their own needle gave them a choice about when to use drugs, rather than their feeling compelled to use drugs immediately whenever a needle was available for sharing.

We, as a society, have to decide to admit that drug use occurs in prisons in the United States (and elsewhere),

that it is a public health problem, and that we have to treat that public health problem if we want to stop inmates from getting infected with HIV and bringing HIV back into the community. Or, we can continue to ignore the problem, because we do not want drugs to be in prisons, because drugs are not supposed to be there, and because we want people to feel deprived in prison, where they are supposed to be receiving punishment.

We can also provide case management when inmates leave prison. Project Bridge was a labor-intensive program in Rhode Island that observed 97 released inmates over 3 years (Rich, *J Urban Health*, 2001). Only 3% of subjects were lost to follow-up, and there was 73% adherence to appointments overall, including 100% adherence to HIV-related appointments, 100% to appointments for the AIDS Drug Assistance Program or otherwise related to AIDS medication, 76% to housing-related appointments, and 37% to employment-related appointments. Ninety-five percent of clients were referred to mental health services, but adherence to those appointments was only 48%, meaning that we need to do better with getting and keeping these people in mental health treatment. In this regard, it is significant that the biggest issue the subjects reported in the

study was trust; the predominant sentiment was their lack of trust of “the system” and fear of actions by health workers that might lead to their reincarceration.

Treatment works. Figure 1 shows data from a small study in the Johns Hopkins Moore Clinic comparing time to receipt of antiretroviral therapy and length of survival in patients receiving treatment for mental disorders versus matched patients with no documentation of mental illness or psychiatric intervention (essentially, a group of individuals with an estimate of > 50% undiagnosed mental illness). A patient in the HIV clinic at Johns Hopkins who is receiving treatment from a psychiatrist is substantially more likely to be receiving antiretroviral treatment—because mental illness treatments improve adherence, both to mental illness treatments and HIV treatments. Although the difference was not statistically significant, there was a trend that patients receiving mental health treatment were also more likely to be alive at the end of the follow-up period. The benefits seen in this small study are not the result of a complex intervention that can never be replicated at some other site; the benefits are really just the result of improved adherence to antiretroviral drug regimens in mentally ill patients who are taking medi-

Table 1. HIV Outcome in Prison-based Needle-exchange Programs

Prison	Switzerland		Germany		Spain	
	Hindelbank	Realta/Cazis	Lingen	Vechta	Basauri, Bilbao	Pamplona
Sex	Women	Men	Men	Women	Men	NA
No. of inmates	110	100	230	170	250	150
Injection drug use, %	39	42	50	50	50	64
Sample size, no.	137	234	83	169	607	115
No. of years studied	2	1	2	2	1	1
No. of syringes distributed	5985	1389	4517	16,390	12,500	NA
Syringes returned, %	100	NA	98.3	98.9	82	NA
Cases of blood-borne virus infection	0	0	0	0	0	0

NA indicates not available. Adapted from Dolan et al, *Addiction*, 2003.

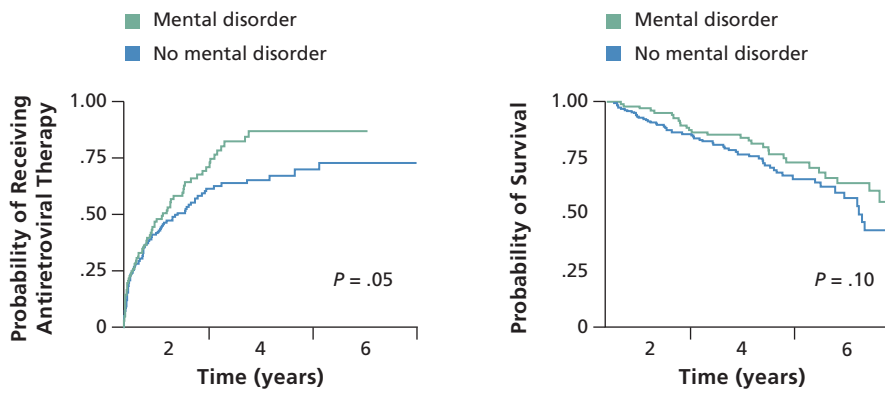


Figure 1. Left: Time to receipt of antiretroviral treatment in patients with versus without documented mental disorders at the Johns Hopkins Moore Clinic. Right: Length of survival among HIV-infected individuals receiving treatment for mental disorders at the Johns Hopkins Moore Clinic versus those with no documented mental disorder or psychiatric intervention.

cations for their mental illness and receiving counseling.

Mental illnesses have always fueled the HIV epidemic (Figure 2). Their effects in this regard have become increasingly apparent as the benefits of prevention and effective treatment have increased in those segments of society that can and do take better care of themselves. The availability of effective treatments for HIV infection and for mental illness means little if affected individuals are not getting them or are not adherent to them. Who are the high-risk individuals? Who are the individuals who engage in risk behaviors? Many of them are in psychiatric clinics, in corrections facilities, in sexually transmitted disease clinics, or are homeless. These are the people we need to target with effective treatments. We all know what happens with mentally ill individuals who come to our clinics and are not

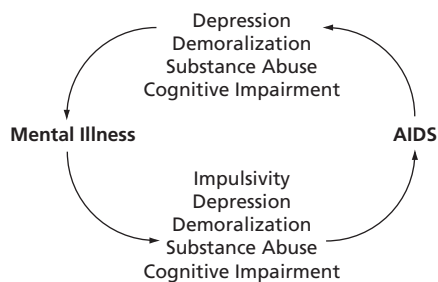


Figure 2. Interrelationship of mental illness and AIDS.

receiving effective treatment for their mental illness: We ask them where they have been and try to prod them to be responsible and keep their appointments, while they point out how hard that is. Few clinics have psychiatrists who work closely with HIV providers, and almost none have psychiatrists on site. Thus, HIV providers can refer patients, but have just as much impact on adherence to mental health treatments as they do to HIV treatments for this ill population.

So, part of the hard work to be done is to bring this message and these data to our legislators, clinic managers, funding and granting entities, and communities and emphasize the urgency of identifying and treating mental illness in these populations. The science and the capitalist system behind the development of effective drug treatments are wonderful; we invent important new drugs and treatments, and those responsible for doing this should be rewarded for it. Advances in health care do not always accompany development of a new drug, however. If we acknowledge that we are a multilayered society, real advances in health care can come when we raise the health-care standards for the low, the disenfranchised, and the no-voice, nonvoting patients who are mentally ill, have been in and out of the corrections system, and have few people invested or interested in their well-being. We can find them if we want to.

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Managing Initiation of Antiretroviral Therapy in a Patient with Chronic Methamphetamine Use and Depression

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Drug toxicities, changes in HIV resistance-mutation profiles, and drug interactions have complicated the selection of antiretroviral regimens. This activity examines strategies for initiating antiretroviral therapy in a newly diagnosed, treatment-naive patient with relapsing substance use and depression. Learners will review current guidelines for starting therapy, compare the advantages and disadvantages of initial drug regimens, and consider the laboratory tests needed to support the selection of an initial regimen.

Managing Oral Health Problems in People with HIV Infection

by David A. Reznik, DDS

A substantial portion of new patients with HIV infection receive an AIDS diagnosis. When diagnosis occurs late, HIV-infected patients are more likely to present with oral diseases that are commonly associated with HIV disease progression. This activity discusses common oral lesions that HIV clinicians encounter in their patients and that can be addressed in the absence of a dental health care professional. This activity also discusses the laboratory test data and medical history information that HIV clinicians should share with dental health care professionals in order to facilitate access to safe and effective oral health care.

Strategic Use of Antiretroviral Drugs in the Patient with Numerous Treatment Failures and Multidrug Resistance

by Harry W. Lampiris, MD, and Elvin H. Geng, MD

Managing HIV treatment-experienced patients has become more complicated than ever owing to the arrival of 2 new classes of antiretroviral agents and half-a-dozen new anti-

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Syphilis in the HIV-infected Patient

by Jeanne M. Marrazzo, MD, MPH

The incidence of syphilis has increased dramatically among HIV-infected persons in the United States. This well-received new *COW* activity introduces learners to screening for sexually transmitted diseases in the HIV-infected patient, interpreting the significance of a reactive nontreponemal serologic test for syphilis, and determining the management of latent syphilis in the HIV-infected patient.

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