

Topics in HIV Medicine®

A publication of the International AIDS Society–USA

Perspectives

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About This Issue

This issue features 3 *Perspective* articles from presentations given at the International AIDS Society–USA continuing medical education course held in May 2009 in Chicago. The first article, based on a presentation by Steven G. Deeks, MD, describes the accelerated aging seen in many people receiving long-term anti-retroviral therapy. The article describes several factors likely to contribute to the persistent inflammation and suboptimal CD4+ gains observed in these patients, and it discusses current research on potential approaches to reducing the risk of non–AIDS-related morbidity and mortality. The second article summarizes a presentation given by Marion G. Peters, MD, on end-stage liver disease in HIV infection. Liver disease is the most common non–AIDS-related cause of mortality in people with HIV disease. The article discusses issues in the management of decompensated liver disease and transplantation considerations for HIV-infected patients. The final article, based on a presentation by Rochelle P. Walensky, MD, MPH, discusses cost-effectiveness data for various HIV disease interventions. Such analyses have been instrumental in the formation of HIV policy in the United States.

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Perspective

Immune Dysfunction, Inflammation, and Accelerated Aging in Patients on Antiretroviral Therapy

Patients receiving long-term antiretroviral therapy are at increased risk of age-associated non-AIDS-related morbidity and mortality compared with HIV-seronegative persons. Despite suppressive antiretroviral treatment, inflammation remains elevated and CD4+ count often remains low, with both measures predicting age-associated events. Several factors likely contribute to persistent inflammation and suboptimal gains during therapy. These include residual HIV replication, persistent virus expression, loss of immunoregulatory cells, collagen deposition, microbial translocation, chronic coinfections, and thymic dysfunction. How these factors influence disease outcomes and how chronic inflammation should be managed during therapy are the focus of intense ongoing investigation. Currently, the most practical advice is to start antiretroviral therapy early and to manage traditional risk factors for non-AIDS-related conditions aggressively. This article summarizes a presentation made by Steven G. Deeks, MD, at the International AIDS Society–USA continuing medical education program in Chicago in May 2009.

The most commonly stated goal of therapy is to prevent AIDS-related complications and prolong life. It might be argued, however, that the real goal of therapy should be to fully restore health and to prolong life in a manner that is not distinguishable from HIV-uninfected persons. The fact that we are now considering such a goal illustrates how successful antiretroviral therapy has been for those patients who can access and adhere to treatment with these drugs.

Current treatment provides the ability for patients to achieve and maintain undetectable levels of plasma HIV RNA and can successfully prevent AIDS-related morbidity and mortality, resulting in increased lifespan for HIV-infected patients. However, it has become evident that patients taking otherwise effective antiretroviral drugs remain at increased risk of non-AIDS-related morbidity and mortality. Many of these conditions are classically associated with the normal aging process but appear to be occurring at an earlier age in HIV-infected persons. These conditions include premature onset of cardiovascular disease, neurocognitive disease, bone disease, and cancer.

Poorer Life Expectancy and Increased Risk of Non-AIDS-Related Conditions in Treated Patients

Depending on when antiretroviral therapy is started, life expectancy for HIV-infected persons in the modern treatment era is approximately 10 years to 30 years less than that for uninfected persons. For example, the number of additional years of life expectancy at age 20 is estimated to be 32 in patients with a CD4+ count nadir of less than 100 cells/ μ L, 42 years in those with a nadir of 100 cells/ μ L to 200 cells/ μ L, and 50 years in those with a nadir of greater than 200 cells/ μ L (Antiretroviral Therapy Cohort Collaboration et al, *Lancet*, 2008; Lohse et al, *Ann Intern Med*, 2007; Lewden et al, *JAIDS*, 2007). According to a prospective study from France, a normal life span can be expected only once a patient has been on effective therapy for several years and obtained a “normal” CD4+ count (> 500 cells/ μ L; Lewden et al, *JAIDS*, 2007).

Why are treated patients dying earlier than their non-HIV-infected peers? Numerous reports have indicated higher rates of non-AIDS-related conditions and events in patients treated for HIV disease than in age-matched control sub-

jects, including cardiovascular disease, cancers, bone fractures and osteopenia, left ventricular dysfunction, liver failure, kidney failure, cognitive decline, and frailty (Klein et al, *JAIDS*, 2002; Hsue et al, *Circulation*, 2004; Mary-Kraus et al, *AIDS*, 2003; Grinspoon et al, *Circulation*, 2008; Triant et al, *J Clin Endocrinol Metab*, 2008; Arnsten et al, *AIDS*, 2007; Odden et al, *Arch Intern Med*, 2007; McCutchan et al, *AIDS*, 2007; Desquilbet et al, *J Gerontol A Biol Sci Med Sci*, 2007). In addition, there are many reports in the popular press regarding vague but not-uncommon complaints about long-term-treated patients feeling “older” than they should. These concerns are difficult to quantify epidemiologically, and may apply to only a small subset of treated patients, but they clearly represent a growing concern among some patients and their advocates (Deeks and Phillips, *BMJ*, 2009).

Contributing Factors

The poorer health and sense of health among patients receiving long-term suppressive antiretroviral therapy is likely related to several factors. Although many of the studies that have examined non-AIDS-related morbidity and mortality have controlled for age, the age of the population of HIV-infected patients is increasing, as is the frequency of age-related conditions. By the year 2015, it is expected that more than 50% of the HIV-infected population in the United States will be over the age of 50 years. Between 2001 and 2005, there were dramatic shifts in the age distribution of HIV-infected persons in the United States, with a reduction in the proportion below age 40 and an increase in the proportion above this threshold (Effros et al, *Clin Infect Dis*, 2008; Figure 1). The real concern, however, is not that the HIV-infected population is getting older (a natural outcome of effective

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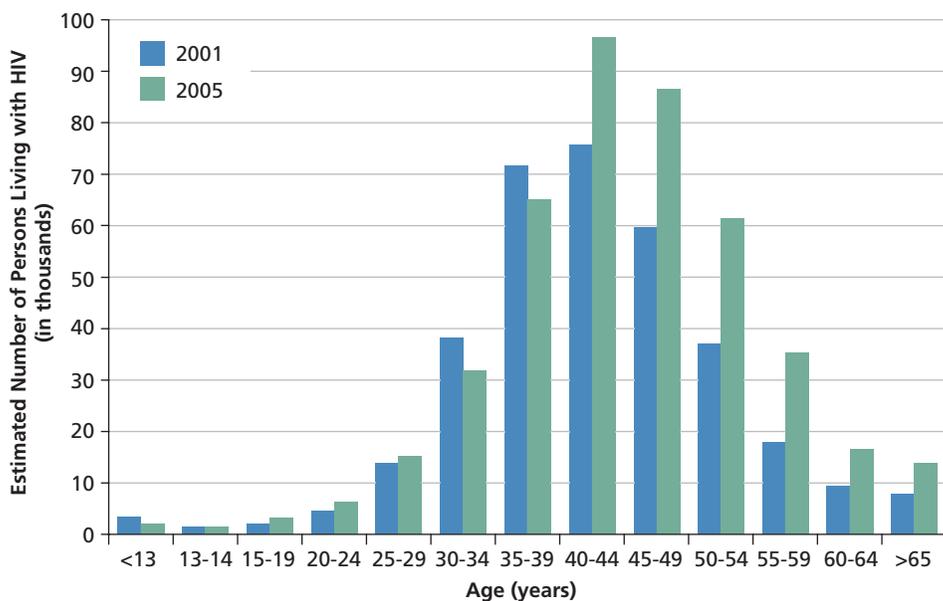


Figure 1. Age distribution of HIV-infected individuals living in the United States. Adapted from Luther and Wilkin, *Clin Geriatr Med*, 2007.

therapy), but that for any given age, HIV-infected persons are at increased risk of age-associated complications.

Also contributing to age-associated complications are the direct toxicities of antiretroviral drugs. A clear example of such effects was provided by the D:A:D (Data Collection on Adverse Events of Anti-HIV Drugs) study, which showed that long-term exposure to protease inhibitor (PI) treatment was independently associated with higher risk of cardiovascular disease (DAD Study Group et al, *N Engl J Med*, 2007). Other antiretroviral drugs may contribute to the aging process by causing renal dysfunction (eg, tenofovir) or heart disease (eg, abacavir).

Another major factor contributing to the non-AIDS-related, age-associated morbidity in treated HIV disease is the high prevalence of traditional health-related risk factors. For example, analysis of the MACS/WHIS (Multicenter AIDS Cohort Study/Women's Interagency HIV Study) population showed higher prevalence of risk factors such as low levels of high-density lipoprotein cholesterol, elevated levels of triglycerides, and smoking in HIV-infected patients than in their uninfected counterparts (Kaplan et al, *Clin Infect Dis*, 2007). Although many cohort studies have attempted to control for the

increased prevalence of these factors, it is nearly impossible to fully address this concern. Hence, how much of the risk of age-associated complications can be attributed to traditional risk factors remains unclear. This question is important, as most of these risk factors are clearly modifiable, whereas most of the HIV-associated factors (immunodeficiency, inflammation) may be difficult to reverse.

It has become increasingly likely, however, that these non-AIDS-related events are more common in HIV disease, after adjustments are made for age, exposure to antiretroviral therapy, and traditional risk factors. An independent role of HIV disease in causing accelerated aging is suggested by findings that levels of inflammation do not normalize during antiretroviral therapy and that elevated inflammation levels and lower on-treatment CD4+ counts both predict risk of non-AIDS-related events.

Inflammation Is Elevated in Treated HIV Disease

Data from the SMART (Strategies for Management of Antiretroviral Therapy) study showed higher levels of the inflammatory or coagulation markers high-sensitivity C reactive protein

(hs-CRP), interleukin-6 (IL-6), D-dimer, and cystatin C in patients with treated HIV disease than in uninfected control subjects (Neuhaus et al, *CROI*, 2009). Among patients on stable antiretroviral therapy in the SMART study compared with uninfected control subjects, the risk of any-cause mortality was statistically significantly increased for elevated IL-6 levels (odds ratio [OR], 2.4; $P = .03$). There were also nonsignificant trends suggesting an association between risk of all-cause mortality and elevated levels of hs-CRP (OR, 2.7; $P = .08$) and D-dimer (OR, 7.1; $P = .08$) (Kuller et al, *PLoS Medicine*, 2008).

Low On-Therapy CD4+ Counts Predict Mortality and Age-Related Events

A robust and growing series of studies indicate that suboptimal CD4+ cell gains in patients receiving antiretroviral

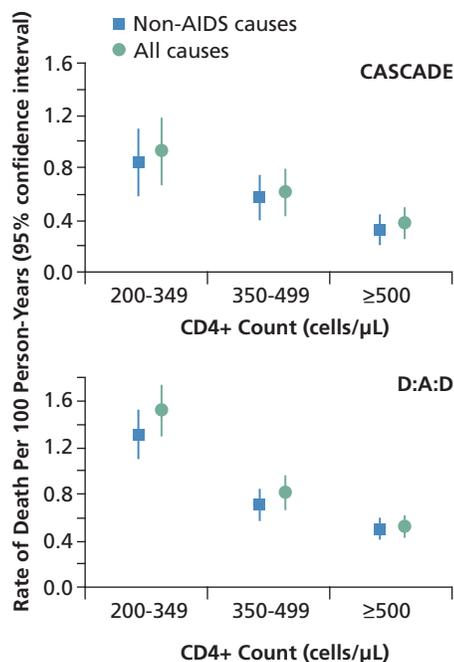


Figure 2. Rate of non-AIDS-related death and all-cause death, with 95% confidence intervals, according to on-treatment CD4+ count in the CASCADE (Concerted Action on Seroconversion to AIDS and Death in Europe) and D:A:D (Data Collection on Adverse Events of Anti-HIV Drugs) studies. Adapted from Phillips et al, *AIDS*, 2008, based on Smit et al, *JAIDS*, 2008, and Neaton and Grund, *Curr Opin HIV AIDS*, 2008.

therapy are associated with a higher risk of morbidity and mortality. For example, the risk of heart disease, liver disease, and non-AIDS-related cancer is higher in treated patients with lower CD4+ cell counts (Weber et al, CROI, 2005; Weber et al, *Arch Intern Med*, 2006; Phillips et al, *AIDS*, 2008; Baker et al, *AIDS*, 2008). Data from both the CASCADE (Concerted Action on Seroconversion to AIDS and Death in Europe) study in antiretroviral-naive patients and the D:A:D study indicate higher risk of death due to non-AIDS-related causes in patients with lower on-treatment CD4+ counts than in those with counts of 500 cells/μL or higher (Figure 2; Phillips et al, *AIDS*, 2008). Although an on-treatment CD4+ count below 500 cells/μL increases risk of non-AIDS-related events, whether risk of such events becomes comparable with the uninfected population if the CD4+ count is increased to and maintained above 500 cells/μL is still unknown.

Suboptimal CD4+ Count Gains Are Common in Treated Patients

Although most patients who start therapy with a CD4+ count above 200 cells/μL eventually achieve a “normal” CD4+ count (generally defined as > 500 cells/μL, considered on the low end of “normal”), many patients who defer therapy until late in disease fail to achieve a robust CD4+ cell gain. For example, recent data from the Center for AIDS Research Center Network of Integrated Clinical Systems (CNICS) indicate that 40% of patients starting treatment with a CD4+ count below 200 cells/μL failed to reach a count of 500 cells/μL over the course of 10 years of suppressive antiretroviral therapy (Kelley et al, *Clin Infect Dis*, 2009; Figure 3). A typical clinical observation is that patients starting treatment at a CD4+ count below 200 cells/μL tend to have a count that plateaus in the 200 cells/μL to 350 cells/μL range.

These findings should be considered in the context that antiretroviral treatment routinely is started at a CD4+ count below 200 cells/μL in developed areas of the world, including the United States. Data from 176 sites in 42

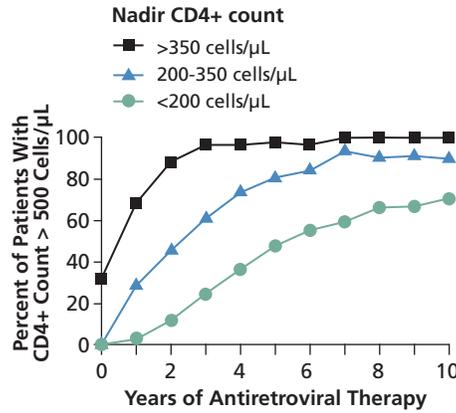


Figure 3. Percentage of patients reaching a CD4+ count in the “normal” range (> 500 cells/μL) over 10 years of treatment, stratified by CD4+ count before initiation of therapy. Adapted from Kelley et al, *Clin Infect Dis*, 2009.

countries for 2003 to 2005 showed that compared with data from 2000, the CD4+ count at which antiretroviral therapy was started remained at approximately 150 cells/μL to 200 cells/μL in developed areas (187 cells/μL in the United States). The starting count was lower in resource-poor areas, although it had increased from 50 cells/μL to 100 cells/μL in sub-Saharan Africa (Egger, CROI, 2007).

Thus, the emerging picture of the health of HIV-infected patients who are being treated successfully with antiretroviral therapy in terms of viral suppression is as follows: lifespan is not normalized by antiretroviral treatment; the risk of age-associated diseases is higher than expected; inflammation remains elevated and predicts age-associated events; and CD4+ count often remains low and predicts age-associated events.

Inflammation and Immunosenescence in HIV Infection

Immunosenescence is a vague and poorly defined concept, but it generally refers to the well-known effects of aging on function of the adaptive immune system. The immune system of the very old (> 70 years of age) is characterized by increased populations of terminally differentiated effector

CD8+ cells (which appear to be resistant to apoptosis), reduced levels of naive CD8+ cells, a reversed ratio of CD4+ to CD8+ cells, increased T-cell activation, increased levels of many inflammatory markers, and reduced T-cell proliferation. Most of these outcomes are accelerated by the presence of chronic persistent infections, with cytomegalovirus (CMV) infection most consistently implicated in the “aging” process. This picture of immunosenescence closely resembles observations in patients receiving long-term antiretroviral therapy, suggesting that ongoing HIV-related immune dysfunction and inflammation during antiretroviral treatment underlies premature aging in HIV-infected persons.

Collectively, these observations support an emerging model that posits that residual inflammation and suboptimal CD4+ count gains along with a hypercoagulable state can result from several ongoing factors. These include residual viral replication, persistent viral expression, the loss of immunoregulatory cells, collagen deposition, microbial translocation, high pathogen load (CMV, HBV, HCV), and thymic dysfunction.

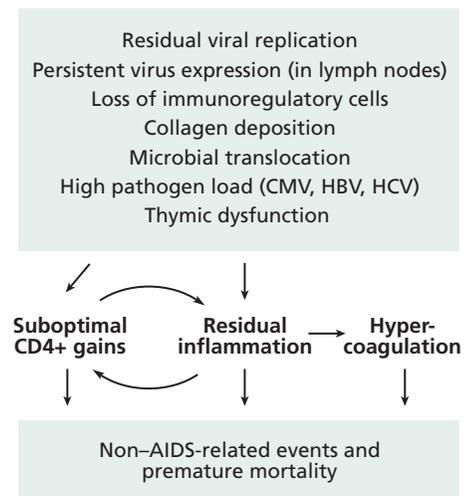


Figure 4. Factors involved in increased risk of premature age-associated non-AIDS-related events in treated HIV disease. CMV indicates cytomegalovirus infection; HBV, hepatitis B infection; HCV, hepatitis C virus infection.

Table 1. Approaches to the Management of “Immunologic Failure” in HIV-Infected Patients

Start antiretroviral treatment early

Aggressively manage traditional risk factors (eg, incorporate use of statins, aspirin, others)

In addition:

Avoid offending antiretroviral medications (including the combination of tenofovir and didanosine)

Treat coinfections (hepatitis C virus, hepatitis B virus)

Consider a ritonavir-boosted, protease inhibitor–based regimen

Consider treatment intensification

Consider immune-based therapies (research studies): CC chemokine receptor 5 (CCR5) inhibitors, interleukin-7, growth hormone

(HCV), or hepatitis B virus (HBV), and thymic dysfunction. How these factors combine to affect CD4+ cell gains, immune function, and early morbidity and mortality is not known.

Can We Prevent or Reduce Inflammation and Accelerated Aging?

What can be done about ongoing inflammation, suboptimal CD4+ count gains, and “accelerated aging” during antiretroviral therapy? Although there are several potential approaches, most are still theoretical and should remain the focus of clinical research studies (Table 1). For now, the most practical approaches may be to start antiretroviral therapy early to prevent potentially irreversible immune dysfunction, including CD4+ loss, and to institute aggressive management of traditional risk factors—for example, use statins, aspirin, or other preventive antiinflammatory treatments. Perhaps antiretroviral therapy–treated HIV disease should be considered an important cardiovascular risk factor like smoking and diabetes that should prompt aggressive risk-factor treatment, irrespective of whether elevated lipid levels or other traditional cardiovascular risk markers are present.

With regard to the other potential approaches to reducing risk of non–AIDS-related morbidity and mortality, there is strong evidence that switching to the combination of tenofovir plus didanosine is associated with CD4+ count declines, apparently reflecting intercellular

toxicity in T cells (Negredo et al, *AIDS*, 2004; Barreiro and Soriano, *J Antimicrob Chemother*, 2006). Some practitioners advocate dose modification when this combination is used, whereas others avoid use of the combination.

As certain coinfections may accelerate the aging process (or exacerbate the inflammatory state), consideration should be given to their treatment. This is particularly true for HBV and HCV infections. Unfortunately, no safe therapy is available for CMV, which is the major persistent infection associated with immunosenescence and age-associated morbidity.

Use of ritonavir-boosted (*lr*), PI-based regimens might be considered to achieve higher CD4+ counts during treatment. Many reports indicate greater increases in CD4+ count with PI/*r* regimens than with non–PI-based regimens, even when virologic response rate with the PI-based regimen is lower. For example, in ACTG (AIDS Clinical Trials Group) 5142, increases in CD4+ count at 96 weeks were 287 cells/ μ L with lopinavir/*r* plus 2 nucleoside analogue reverse transcriptase inhibitors (nRTIs), 273 cells/ μ L with the nonnucleoside analogue reverse transcriptase inhibitor (NNRTI) efavirenz plus lopinavir/*r*, and 230 cells/ μ L with efavirenz plus 2 nRTIs ($P = .001$ across treatments) despite the finding that the proportion of patients with plasma HIV RNA levels below 50 copies/mL was lower in those receiving the PI-based regimens (Riddler et al, *N Engl J Med*, 2008). Although the strategy has not been examined in

a clinical trial, it may make sense to consider switching patients with “stagnant” CD4+ counts from NNRTI-based regimens to PI/*r*-based regimens to attempt to achieve additional gains in the CD4+ count.

Similar findings have been made with the entry inhibitor maraviroc in the MERIT (Maraviroc Versus Efavirenz Regimens as Initial Therapy) trial, in which the combination of maraviroc plus fixed-dose zidovudine/lamivudine produced a statistically significantly greater increase in CD4+ count (169 vs 142 cells/ μ L) and CD8+ count at 48 weeks than did efavirenz plus zidovudine/lamivudine, despite a lower virologic response rate (Saag et al, *IAC*, 2007). Possibly, by blocking the CC chemokine receptor 5 (CCR5) coreceptor on T cells, maraviroc acts to prevent T cells from migrating to gut lymphoid tissue, where they may be killed by HIV. The strategy of intensified therapy including maraviroc is now being evaluated in patients with poorer CD4+ responses with antiretroviral therapy.

The phenomenon of ongoing viral production under suppressive antiretroviral therapy is also being investigated. Use of a super-sensitive assay in a University of California San Francisco cohort of patients achieving undetectable viral load on a standard assay during antiretroviral treatment showed that over years of follow-up, virus was detectable at approximately 80% of the measurement time points (Hatano et al, *CROI*, 2009). This evidence of ongoing viral production, and perhaps replication, suggests that adding another drug to current regimens may be a rational strategy for further reducing viral expression and potentially reducing inflammation. This strategy is being examined using the integrase inhibitor raltegravir.

A strategy of increasing CD4+ count that has not proved successful in improving clinical outcomes is the use of interleukin-2 (IL-2), which has long been recognized to boost CD4+ counts. The large-scale ESPRIT (Evaluation of Subcutaneous Proleukin [aldesleukin] in a Randomized International Trial) showed that although treatment including IL-2 produced an average 160-cell/ μ L

increase in CD4+ count versus control treatment over 7 years of follow-up ($P < .001$), there was no difference in rates of opportunistic conditions or death in the 2 groups (Losso et al, CROI, 2009). The CD4+ cells produced under IL-2 treatment are of an unusual phenotype, are long-lived, and may not be normal, characteristics that may account for the absence of benefits observed with IL-2 treatment.

The definitive proof of the failure of IL-2-induced CD4+ count boost to improve clinical outcome should not affect investigation of interleukin-7 (IL-7). Phase I trials of IL-7 have also shown impressive, rapid increases in CD4+ count (Levy et al, *J Clin Invest*, 2009). The CD4+ cells produced with IL-7 treatment include central memory cells and naive cells, deficits in which are thought to account for a major portion of the immune dysfunction in many patients treated long-term.

Growth hormone has also been shown to increase CD4+ count, apparently by stimulating thymic production of naive cells (Napolitano et al, *J Clin Invest*, 2008). However, growth hormone is not being used widely in patients receiving antiretroviral treatment, in part because of its toxic effects and expense.

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

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Suggested Reading

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Perspective

End-Stage Liver Disease in HIV Disease

Liver disease is the most common non-AIDS-related cause of mortality in HIV-infected patients. HIV-infected patients with chronic liver disease progress more rapidly to cirrhosis, and those with hepatitis B virus or hepatitis C virus coinfection progress more rapidly from decompensation to death and are at increased risk of death from end-stage liver disease. With improvements in health associated with antiretroviral therapy, liver transplantation is increasingly an option in HIV-infected patients with end-stage liver disease. Elements of management of decompensated liver disease, including staging, treatment of variceal hemorrhage and ascites, and considerations in transplantation in the HIV-infected patient are discussed. This article summarizes a presentation made by Marion G. Peters, MD, at the International AIDS Society–USA continuing medical education program held in Chicago in May 2009. The original presentation is available as a Webcast at www.iasusa.org.

Liver disease is the single greatest cause of non-AIDS-related death in patients with HIV disease, accounting for a greater proportion of deaths than cardiovascular disease or non-AIDS-related cancers (Weber et al, *Arch Intern Med*, 2006). Progression to cirrhosis is more rapid in HIV-infected patients with chronic liver disease, and end-stage liver disease (ESLD) is now common. A major contributor to ESLD in HIV-infected patients is the high rate of coinfection with hepatitis C virus (HCV) or hepatitis B virus (HBV), estimated at 30% and 10%, respectively.

Progression to cirrhosis is accelerated in coinfecting patients, and risk of death due to ESLD is markedly increased by coinfection. One recent study showed a dramatic reduction in time from first decompensation to death for patients with HIV and HCV coinfection versus those with HCV infection alone, with 54% versus 74% surviving 1 year, 40% versus 61% surviving 2 years, and 25% versus 44% surviving 5 years, respectively (Pineda et al, *Hepatology*, 2007). Another showed that proportions of deaths due to ESLD in HIV-infected persons were 1.2% in those with neither HBV nor HCV coin-

fection, 22% in those with HBV coinfection, 31% in those with HCV coinfection, and 44% in those with HBV and HCV coinfections (Salmon-Ceron et al, *J Hepatol*, 2005). Immune reconstitution with antiretroviral therapy has had a substantial effect in reducing risk of liver-related mortality associated with HCV infection compared with that in patients receiving early antiretroviral therapy or those receiving no treatment before the advent of antiretroviral therapy (Qurishi et al, *Lancet*, 2003). Largely as a result of improvement in

health and life expectancy with antiretroviral treatment, orthotopic liver transplantation is increasingly considered as an option in HIV-infected patients with liver disease. In addition, successful therapy for HBV and HCV infections can reverse fibrosis and halt progression to cirrhosis and in some cases even reverse cirrhosis and its complications.

Natural History of End-Stage Liver Disease and Disease Staging

Chronic liver disease from any cause (eg, alcohol, HBV or HCV coinfection, nonalcoholic steatohepatitis, or cholestatic or autoimmune causes) results in increasing fibrosis, with a proportion of patients progressing to compensated cirrhosis and a proportion of these progressing to hepatocellular carcinoma (HCC) or decompensated disease with variceal hemorrhage, ascites, encephalopathy, or jaundice. Patients with decompensation are more likely to die. HCC increases risk of decompensation and risk of death in those with decompensation. Over-

Table 1. Measures Used in Child-Pugh-Turcotte Scoring and Number of Points Contributing to Score^a

Measure	Number of Points		
	1 (normal)	2	3
Hepatic encephalopathy (grade)	None	1-2	3-4
Ascites	None	Slight	Moderate
Bilirubin (mg/dL)	<2	2-3	>3
Albumin (g/L)	>3.5	2.8-3.5	>2.8
Prothrombin time prolongation (seconds) OR International normalized ratio	<4 <1.7	4-6 1.7-2.3	>6 >2.3

^aChild-Pugh-Turcotte scoring categories: class A, total of 5 or 6 points; class B, 7 to 9 points; class C, > 9 points. Adapted from Pugh, *Gut*, 1999, and Weisner et al, *Gastroenterology*, 2003.

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all, an estimated 5% to 7% of patients with compensated cirrhosis progress to decompensated disease each year. Currently, the best predictor of decompensation is a hepatic venous pressure gradient (HVPG) of greater than 10 mm Hg; however, measurement of HVPG requires an invasive technique (placing a catheter through the heart and wedging it in the hepatic vein) and thus is not performed routinely outside of several US centers.

The Child-Pugh-Turcotte (CPT) score and Model for End-Stage Liver Disease (MELD) score are widely used tools for assessing disease severity and predicting death in patients with decompensated cirrhosis. The CPT score, developed in the 1970s to assess risk of death after variceal bleeding or portacaval shunting, includes grading of encephalopathy and ascites, albumin level, bilirubin level, and prothrombin time or international normalized ratio (INR; Table 1). Class A (CPT score, 5–6) indicates well-compensated cirrhotic disease, with progressively worse disease indicated by classes B (score, 7–9) and C (score, >9).

The MELD scoring system, developed subsequently at the Mayo Clinic, avoids the subjectivity involved in grading encephalopathy and ascites by including only bilirubin level, INR, and creatinine level in a mathematic model (Table 2). The initial study of this scale showed that it predicted 3-month mortality after transjugular intrahepatic portosystemic shunting (TIPS), and subsequent studies showed it to be a better predictor of survival of patients on the liver transplant waiting list than was the CPT score. For approximately the past 10 years, the MELD score has been used to determine order on the liver transplantation waiting list. Increases in INR and creatinine have a greater effect on the overall score; for example, starting with a normal score of 6, a doubling of bilirubin level would increase the score to 10, a doubling of INR to 20, and a doubling of creatinine level to 27. A further increase in INR would bring the score to 31, which is the current score needed for blood-type-O patients to receive a transplant in many large centers; non-blood-

Table 2. Examples of Model for End-Stage Liver Disease (MELD) Scoring

Measure	Value		
Bilirubin (mg/dL)	2	5	5
International normalized ratio	1.1	2.0	2.0
Creatinine (mg/dL)	1.0	1.0	2.0
MELD score	10	20	27

type-O patients are eligible for transplantation at lower scores (in the 20s) at most large centers.

Cirrhosis staging also predicts mortality. Stage 1 is compensated cirrhosis with absence of varices, stage 2 is compensated cirrhosis with varices, stage 3 is decompensated cirrhosis and ascites without variceal hemorrhage, and stage 4 is decompensated cirrhosis and variceal hemorrhage with or without ascites. Data from a large cohort of untreated patients indicate 1-year mortality rates of 1% for patients in stage 1 disease, 3% in stage 2, 20% in stage 3, and 57% in stage 4.

Varices and Variceal Bleeding

All patients with cirrhosis should be screened for varices by upper endoscopy and treated prophylactically if varices are present. Primary prophylaxis for varices of grade 2 or higher consists of treatment with a nonspecific beta-blocker (eg, propranolol) to decrease heart rate by 10%.

Nonspecific treatment of variceal hemorrhage includes antibiotics (which improve survival) and resuscitation aimed at achieving a hemoglobin level of 9 g/dL (more vigorous resuscitation might serve only to replenish the bleeding varices). Factors associated with increased risk of death within 6 weeks in patients with variceal bleeding in decompensated disease include a MELD score of 18 or greater, the use of 4 or more units of packed red blood cells in the first 24 hours, and active bleeding at endoscopy. Specific therapies for acute variceal hemorrhage include vasoconstrictors (eg, somatostatin, terlipressin, vapreotide, octreotide) given for 2 days to 5 days in an intensive care unit. Endoscopic variceal

band ligation (EVL) to remove varices is now preferred over sclerotherapy, which is associated with a higher risk of esophageal stricture.

If these measures fail, TIPS may be performed. TIPS has largely replaced selective splenorenal shunting, which is now infrequently performed. For prevention of variceal recurrence, the combination of a nonselective beta-blocker (eg, propranolol) and EVL is superior to EVL alone, with a rebleeding rate of 12% to 14% observed with the combination versus 29% to 38% with EVL alone. The effect of vasoconstrictors in this setting is to reduce splanchnic flow and pressure disproportionately to the reduction in blood pressure, with a goal of reducing the pulse rate by 10% (Table 3). In contrast, TIPS or another shunting procedure results in increased flow while markedly reducing resistance and portal pressure.

Ascites

The increase in intrahepatic resistance in cirrhosis leads to portal hypertension, splanchnic and systemic vasodilation, a reduction in effective arterial blood volume, activation of neurohumoral systems, and sodium retention and thus to ascites (Figure 1). Interventions in this cascade of events include TIPS to reduce portal hypertension, improvement of effective arterial blood volume with albumin or peritoneovenous shunting, use of spironolactone with or without furosemide to reverse sodium retention, and large-volume paracentesis or peritoneovenous shunting to reverse ascites. When TIPS is used for variceal bleeding, portal pressure drops promptly (with bleeding absent when the pressure falls below 12 mm Hg), but as-

Table 3. Effects of Variceal Bleeding Therapies

Therapy	Effect on Portal Circulation
Vasoconstrictors (eg, beta-blockers)	Decrease flow
Venodilators (eg, nitrates) ^a	Mild decrease in resistance and portal pressure
Vasoconstrictors, venodilators	Decrease portal pressure
Endoscopic therapy	No effect
Transjugular intrahepatic portosystemic shunting/shunt surgery	Marked decrease in resistance and portal pressure

^aAlthough nitrates theoretically act by decreasing resistance, they produce a decrease in portal flow via a decrease in mean arterial pressure.

Table derived from Garcia-Tsao et al, *Am J Gastroenterol*, 2009.

cites, when present, may not reverse for some 4 weeks to 6 weeks. Thus, although portal hypertension is clearly important in the generation of ascites, simply reducing portal pressure is not sufficient for prompt reversal.

Ascites is staged, by order of increasingly abnormal circulatory state, as diuretic-responsive ascites, refractory ascites, hyponatremia, or hepatorenal syndrome (HRS). Treatment of diuretic-responsive ascites includes sodium intake restriction. Patients should ingest less than 2 g of sodium per day, and intake can be checked by measuring sodium in the urine. If patients report absence of response to diuretics and have 60 mEq of sodium in the urine, they probably need information regarding limiting the salt content of their food. (Unfortunately, the bottom line in this regard is very close to “if it tastes good, don’t eat it.”) Treatment also includes spironolactone at a starting dose of 75 mg to 100 mg and furosemide at a starting dose of 20 mg to 40 mg. Spironolactone increases serum potassium and furosemide reduces it, and the effects of the 2 drugs need to be balanced to keep potassium at a normal level. Doses of spironolactone can be increased up to 300 mg to 400 mg if necessary.

With progressive decompensation, ascites becomes refractory. Treatment of refractory ascites may involve large-volume paracentesis with 25% albumin (50 mL/L); that is, for every liter of fluid taken off the patient, there must be replacement of 50 mL of 25% albumin, otherwise the patient will become se-

verely catabolic. As an alternative, TIPS can be performed. Although TIPS is associated with greater transplant-free survival than is paracentesis, it also has a much higher rate of hepatic encephalopathy. The risk of hepatic encephalopathy reflects the fact that the shunting of blood away from the liver to the systemic circulation permits toxins and other substances from the gut (that would ordinarily be metabolized by the liver) to be delivered to the brain.

The goal of TIPS is to reduce portal pressure to below 12 mm Hg, and the procedure is effective in approximately 80% of patients. There have been a few reports of good outcomes with the combination of albumin with the vasoconstrictors midodrine and octreotide. Experimental treatments include clonidine and vasopressin-2 receptor antagonists.

In hyponatremia, treatment consists of fluid restriction and vasopressin-2 receptor antagonists or midodrine. Hypertonic saline should not be used; patients with hyponatremia have normal levels of total body sodium with massive fluid overload, and hypertonic sodium exacerbates the problem.

HRS results from renal vasoconstriction (characterized by decreased cortical flow and increased medullary flow) in response to vasodilation and a marked reduction in effective arterial blood volume. Acute renal failure occurs in 14% to 25% of hospitalized patients with cirrhosis. HRS is the primary form of prerenal failure and accounts for 60% to 80% of cases, with acute tubular necrosis accounting for 20% to 40%. The rapidly progressive form of HRS (type 1) results in acute renal failure within 2 weeks and is associated with a doubling of serum creatinine level to greater than 2.5 mg/dL or halving of creatinine clearance to below 20 mL/min. It occurs in patients with refractory ascites, hyponatremia, or both. Prognosis is less than 50% survival at 1 month. The slower-progressing form of HRS (type 2) is characterized by

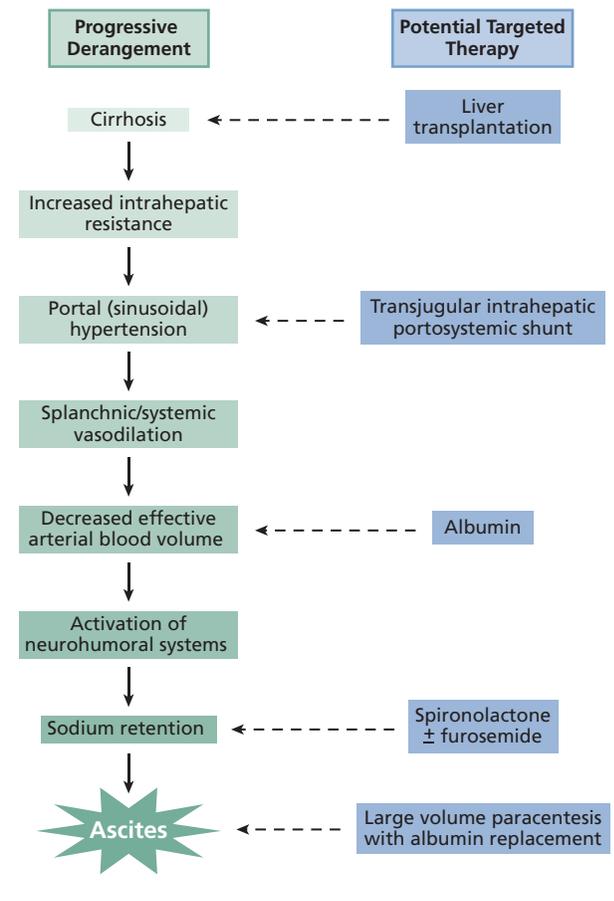


Figure 1. Diagram of the progressive derangement resulting from worsening cirrhosis, indicating potential targeted therapies for management of each stage associated with ascites formation. Adapted from Ring-Larsen and Henriksen, *Semin Liver Dis*, 1986.

an increase in serum creatinine level to greater than 1.5 mg/dL (which may be precipitated by excessive diuresis of patients), creatinine clearance of less than 40 mL/min, and urine sodium level of less than 10 mEq, and it is associated with ascites that is unresponsive to treatment with diuretics. Median survival of patients with type 2 HRS is approximately 6 months. Treatment for HRS consists of liver transplantation. In type 2 HRS associated with extreme splanchnic and systemic vasodilation, treatment with midodrine and octreotide may be successful in reversing vasodilation; albumin is given to increase intravascular volume. These measures rarely have benefit in type 1 HRS. Dialysis is performed in patients with type 1 HRS who are on the transplant waiting list; many of these patients are hypotensive, cannot tolerate intermittent hemodialysis, and are thus treated with continuous veno-venous hemodialysis in an intensive care unit.

Spontaneous Bacterial Peritonitis

Spontaneous bacterial peritonitis (SBP) is the most common type of bacterial infection in hospitalized patients, with *Escherichia coli* the most common pathogen. Clinical suspicion is raised by unexplained encephalopathy, jaundice, and worsening renal failure. In less than 50% of cases, there is fever, abdominal pain or tenderness, and leukocytosis. Diagnosis is made by tapping the ascites—that is, taking off 20 mL to 30 mL of fluid—and performing a white blood cell (WBC) count and culture. For a count greater than 500 WBCs/ μ L or a polymorphonuclear cell count greater than 250/ μ L, antibiotic treatment should be started immediately, prior to receipt of culture results. For culture, samples should be placed in blood culture bottles at the bedside because positive findings are made far more frequently using this approach than by sending the culture to the laboratory. Gram staining is not useful.

Initial treatment is with cephalosporins, with adjustment based on sensitivity testing results. Renal dysfunction is the main cause of death. Intravenous albumin administration can pre-

vent HRS and death in patients with a serum bilirubin level greater than 4 mg/dL, serum creatinine level greater than 1 g/dL, or blood urea nitrogen level greater than 30 mg/dL. Recurrence can be prevented by treatment with ciprofloxacin, trimethoprim-sulfamethoxazole, or norfloxacin. Primary prophylaxis with weekly ciprofloxacin is warranted in patients with decompensation and ascites and may be advisable in any patient with a MELD score greater than 9.

Hepatic Encephalopathy

Hepatic encephalopathy is classified as episodic, persistent, or minimal (previously, acute, chronic, and subclinical). It results from a combination of portosystemic shunting and failure to metabolize neurotoxic substances. The nature of these substances remains unclear after decades of research. Ammonia is not *the* substance but remains the most important neurotoxic substance that can be measured in the blood. Ammonia levels actually correlate poorly with stage of encephalopathy, although high levels of arterial ammonia do correlate with risk of death in patients with fulminant hepatic failure.

Precipitants of encephalopathy include infection (eg, SBP), gastrointestinal bleeding (ie, increased protein load in the gut), electrolyte imbalance, portal vein thrombosis, worsening liver disease, and shunting. Treatment is aimed at reducing production of ammonia (and other toxins) from the colon through use of nonabsorbable disaccharides (eg, lactulose, lactitol, lactose) and nonabsorbable antibiotics such as neomycin and rifamixin; data indicate that rifamixin is less absorbable than neomycin. Protein restriction, once a common treatment, is no longer recommended because it promotes protein degradation, can worsen nutritional status, and can decrease muscle mass when maintained for long periods.

Hepatocellular Carcinoma Monitoring

All patients with cirrhosis should be monitored for HCC. HCC can occur in the absence of severe fibrosis or cirrho-

sis in HBV disease; thus patients with HBV infection who are older (eg, > 40 years) or have a family history of cancer should also undergo screening. The screening strategy consists of alpha-fetoprotein testing and ultrasonography every 6 months to 12 months (every 6 months in patients on the transplant waiting list), with quadruple-phase computed tomography for confirmation of abnormalities. The relative infrequency of ultrasonographic monitoring is based on the relatively low rate of progression from cirrhosis to HCC (approximately 1%–4% per year) and the relatively slow growth rate of HCC tumors (estimated doubling time, 136 days).

Liver Transplantation in HIV-Infected Patients

The indication for liver transplantation, in both HIV-infected and noninfected patients, is development of decompensation (ascites, variceal hemorrhage, hepatic encephalopathy), which is associated with a median survival of 1.5 years. Eligibility for transplantation is based on MELD score and serum sodium level. These criteria likely underestimate the need for transplantation in patients with chronic encephalopathy, hepatic hydrothorax, hepatopulmonary syndrome, or portopulmonary hypertension.

Liver transplantation is now more frequently considered in HIV-infected patients with chronic liver disease because of improvements in health associated with antiretroviral therapy and reflected in reduced mortality, reduced incidence of opportunistic infections, and reduced hospitalization rates from HIV. Immunosuppressive treatment for transplantation (eg, cyclosporine, mycophenolate mofetil, rapamycin) may also have anti-HIV effects. In addition, better prophylaxis for opportunistic infections is now available.

In HIV-infected patients who have undergone liver transplantation, recurrent HBV infection is controlled with combination nucleoside or nucleotide analogue reverse transcriptase inhibitors and HBV immune globulin, such that posttransplantation survival in patients coinfecting with HIV and HBV

is similar to that in HBV-monoinfected patients. Recurrent HCV infection, however, is a serious problem, with patients coinfecting with HIV and HCV having a higher risk of morbidity and mortality from recurrent HCV infection than have patients with HCV monoinfection.

Human papilloma virus (HPV)-associated anal cancer is another major concern. Patients with low-grade cellular abnormalities have progressed to anal cancer during immunosuppression for liver transplantation, and thus patients should be carefully monitored for HPV-associated changes before transplantation. Similarly, Kaposi sarcoma is a major concern, with transplantation not advised in patients with systemic disease. Patients receiving protease inhibitor–based antiretroviral regimens require major adjustments in dosing of calcineurin inhibitors (eg, cyclosporine, tacrolimus). In this regard, close collaboration between HIV physicians and transplant physicians is necessary to avoid drug interactions that pose the risk of organ rejection or cal-

cieneurin toxicity, with a major danger being failure to communicate changes in antiretroviral therapy to the transplant team.

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

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Suggested Reading

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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 Anti-retroviral Treatment Failure

David M. Margolis, MD, FACP, 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.

Pregnancy Planning and Preconception Health Care for HIV-Infected Individuals and Couples

Erika Aaron, MSN, CRNP, and Shannon M. Criniti, MPH
Level: Advanced

Owing to effective antiretroviral therapy, many HIV-infected individuals and couples are choosing to have children. This activity discusses a comprehensive preconception plan of health care for HIV-infected women of child-bearing age, contraception choices, and promoting safer conception in HIV-infected women and serodiscordant couples who desire pregnancy. Learners will identify interactions between antiretroviral drugs and hormonal contraceptives and be able to explain assisted reproduction methods such as sperm washing that reduce the risk of HIV transmission to the noninfected partner.

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Perspective

Cost-Effectiveness of HIV Interventions: From Cohort Studies and Clinical Trials to Policy

Incremental cost-effectiveness ratios quantify the additional cost of an intervention relative to the additional benefit associated with its use. Whether an intervention is considered cost-effective depends largely on policy decisions regarding whether the additional benefit is worth the additional cost in the context of competing needs for resources. In the United States, cost-effectiveness analyses have been instrumental in guiding changes in HIV policy supporting antiretroviral therapy, genotypic resistance testing, and expanded programs for HIV screening. The cost-effectiveness of HIV screening compares favorably with that of accepted screening practices for other chronic diseases. This article is a summary of a presentation made by Rochelle P. Walensky, MD, MPH, at the International AIDS Society-USA Chicago program held in May 2009. The original presentation is available as a Webcast at www.iasusa.org.

Mathematical simulation models for quantifying benefits and costs of interventions in HIV disease are important tools for assessing the impact of care from a public health perspective and for informing policy on expenditure of health care resources. Because the models project both efficacy and costs, these tools allow assessment of cost-effectiveness of a variety of interventions, from opportunistic infection prophylaxis and antiretroviral treatment to use of genotypic assays and screening for HIV infection.

Survival Benefit and Cost of HIV Care

A computer simulation model of HIV disease and treatment, the Cost-Effectiveness of Preventing AIDS Complications (CEPAC) model, has been used to estimate survival benefits of HIV interventions, the costs of the interventions, and their incremental cost-effectiveness ratios. To assess benefits associated with different treatment interventions for patients with AIDS, survival was examined according to treatment “eras.” Each era was defined as a period during which an interven-

tion was considered standard of care. To characterize improvements in antiretroviral treatment efficacy over time, antiretroviral therapy was subdivided into 4 separate eras. Table 1 shows the per-person and total survival benefits

for treated patients with AIDS compared with untreated disease during these eras. The study projects that patients diagnosed with AIDS in antiretroviral therapy era 4 (2003) have a survival benefit of 160 months compared with patients with untreated disease (Walensky et al, *J Infect Dis*, 2006). Overall, the study estimated that by 2005, almost 3 million life-years had been saved due to AIDS therapy alone. Such per-person survival benefits associated with AIDS treatment exceed reported gains associated with treatment interventions for many other chronic diseases in the United States (Figure 1).

The CEPAC model has also been used to estimate costs of HIV care (Schackman et al, *Med Care*, 2006). Using data from a cohort of people with

Table 1. Per-Person Survival Benefit in AIDS Patients by Treatment Era

Years	Intervention	Per-Person Survival Benefit (months)	No. of Patients Diagnosed and Entering Care	Total Survival Benefit (years)
1989-1992	PCP prophylaxis	3.1	158,370	40,912
1993-1995	PCP prophylaxis + MAC prophylaxis	24.4	226,458	460,465
1996-1997	PCP prophylaxis + MAC prophylaxis + ART Era 1	93.7	72,716	567,788
1998-1999	PCP prophylaxis + MAC prophylaxis + ART Era 2	132.6	52,702	582,359
2000-2002	PCP prophylaxis + MAC prophylaxis + ART Era 3	138.8	71,946	832,179
2003	PCP prophylaxis + MAC prophylaxis + ART Era 4	159.9	24,780	330,189
Total				2,813,892

ART indicates antiretroviral therapy; Eras 1-4, periods characterized by improvements in antiretroviral therapy over time; MAC, *Mycobacterium avium* complex; PCP, *Pneumocystis jiroveci* pneumonia. Adapted from Walensky et al, *J Infect Dis*, 2006.

Dr Walensky is associate professor of medicine at Harvard Medical School.

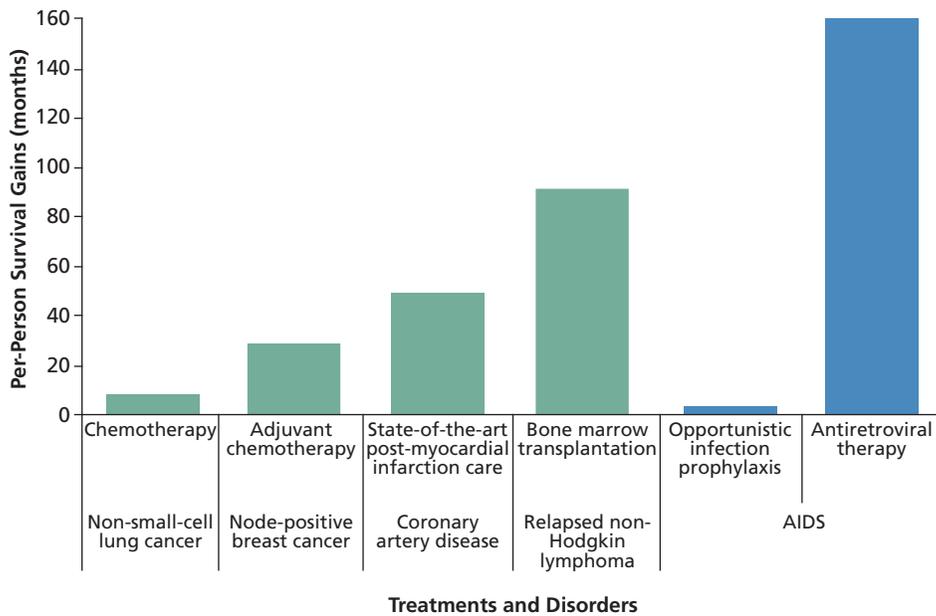


Figure 1. Per-person survival gains with treatment in patients with AIDS compared with gains associated with interventions for other common diseases in the United States. Adapted from Walensky et al, *J Infect Dis*, 2006.

HIV infection with a mean CD4+ count of 310 cells/ μ L and an average projected life expectancy of 24.2 years, the undiscounted lifetime cost of care was estimated to be \$618,900 (discounted cost \$385,200), with antiretroviral therapy accounting for 77% of the cost and inpatient costs for 10%.

Cost-Effectiveness of HIV Care

To calculate the incremental cost-effectiveness of an intervention, analyses must consider the added efficacy (generally measured in years of life saved [YLS] or quality-adjusted life-months or -years [QALM or QALY]) and the additional costs of the intervention. The cost-effectiveness ratio is then calculated with incremental costs in the numerator and incremental benefits in the denominator (\$/QALY). An intervention may be considered cost-effective if the additional benefit provided by the treatment is considered “worth” the additional cost. The World Health Organization (WHO) Commission on Macroeconomics and Health (WHO, 2009) suggested that interventions may be considered very cost-effective when the cost-effectiveness ratio (\$/QALY) is less than 1 times the

per-capita gross domestic product (GDP) for an individual country and cost-effective when the ratio is less than 3 times the per-capita GDP. As a point of reference, the estimated GDP per capita in the United States in 2008 US dollars (USD) is \$46,500 (International Monetary Fund, 2008).

Is antiretroviral therapy cost-effective in the United States? In 2001, Freedberg (principal investigator of the CEPAC group) and colleagues analyzed the cost-effectiveness of antiretroviral therapy. This analysis simulated patients in a clinical trial setting (Dupont 006) and patients in a published clinical cohort from the Johns Hopkins Moore (HIV) Clinic (Freedberg et al, *N Engl J Med*, 2001). The clinical trial population had a mean CD4+ count of 350 cells/ μ L and was intended to examine the antiretroviral therapy impact in a highly motivated, healthier patient population characteristic of clinical trial enrollees. In contrast, the published cohort had a mean CD4+ count of 217 cells/ μ L and simulated patients from the setting of a “real world” inner-city clinic. In the clinical trial population, projected annual costs were \$59,790 (in 1998 USD) for patients not receiving antiretroviral therapy versus \$94,290

for those receiving treatment with efavirenz/zidovudine/lamivudine, and projected QALM values were 47.52 versus 79.56, respectively, yielding a cost-effectiveness ratio (\$/QALY) of approximately \$13,000. In the simulation of the clinical cohort, per-person costs were projected to be \$54,150 for patients not receiving therapy versus \$80,460 for those receiving treatment with indinavir/zidovudine/lamivudine, and projected QALM values were 35.04 versus 53.16, respectively, yielding a cost-effectiveness ratio of approximately \$17,000 per QALY. In both of these settings, antiretroviral therapy may be considered very cost-effective.

Cost-effectiveness analysis of genotypic resistance testing helped motivate guideline development regarding the use of this test in clinical practice (Weinstein et al, *Ann Intern Med*, 2001). Analysis of use of genotypic resistance testing at the time of HIV treatment failure showed costs of \$90,360 with no testing versus \$93,650 with testing (in 1998 USD) and QALM values of 60.9 versus 63.1, respectively. These values yielded a cost-effectiveness ratio of \$17,900 per QALY. The cost increase associated with testing reflects more than the then approximately \$400 cost of the test; most of the increase comes from the cost of additional antiretroviral treatment during the duration of life added by use of the intervention.

Subsequently, genotypic resistance testing was also shown to be cost-effective in antiretroviral therapy-naïve patients (Sax et al, *Clin Infect Dis*, 2005). An analysis was performed over a range of assumptions of prevalence of major HIV drug resistance mutations of 0.25% to 10.0% and for the possible genotypic test costs of \$200, \$400, and \$800. Cost-effectiveness ratios were within the range likely to be considered cost-effective except at combinations of the highest test costs and the lowest prevalences of major resistance mutations. At the actual estimated prevalence of major mutations of 8.3%, the incremental cost associated with testing was \$2000 and the incremental increase in life expectancy was 1.0 QALM, yielding

a cost-effectiveness ratio of \$23,900 per QALY at a test cost of \$400 (\$21,600/QALY at test cost of \$200; \$28,600/QALY at test cost of \$800).

Cost-Effectiveness of HIV Screening

Table 2 shows cost-effectiveness ratios for several HIV-related interventions and for screening programs for other chronic diseases including breast cancer, colon cancer, and diabetes that are currently considered standard of care in the United States. The ratios for HIV screening in inpatients and in high-risk outpatient populations compare favorably with ratios for other accepted

screening programs. Although cost-effectiveness ratios differ according to the models and assumptions employed, several studies of HIV screening in the outpatient setting have generally yielded consistent results at the policy level. Paltiel and colleagues from the CEPAC group (*N Engl J Med*, 2005) found that at a 1% prevalence of undiagnosed HIV infection in the outpatient setting, routine testing every 5 years had a ratio of \$71,000 per QALY, whereas Sanders and colleagues (*N Engl J Med*, 2005) found at the same prevalence a ratio of \$41,700 per QALY for routine screening. In an updated analysis, Paltiel and colleagues (*Ann Intern Med*, 2006) reported that with inclusion of trans-

mission effects (fewer transmissions associated with increased case detection), routine screening in a population with a prevalence of undiagnosed HIV infection of 0.2% had a cost-effectiveness ratio of \$50,000 per QALY. These findings contributed to the rationale for recommendations for routine HIV screening in the United States (Branson et al, *MMWR Recomm Rep*, 2006).

Figure 2 shows cost-effectiveness ratios of HIV screening at different levels of the prevalence of undiagnosed HIV infection in the population and at different test costs. At a baseline test cost of \$26 (indicated by squares), the cost-effectiveness ratio remains below \$50,000 per QALY for all prevalences of undiagnosed HIV infection ranging from 0.1% to 100%. Even at test costs as high as \$104 (eg, for testing plasma HIV RNA level), cost-effectiveness ratios are below \$100,000 per QALY in the prevalence range examined. The data also show that once a 1% prevalence of undiagnosed HIV infection is exceeded, the cost-effectiveness ratio plateaus at about \$36,000 per QALY.

These findings reflect both that the cost-effectiveness ratio for state-of-the-art HIV care (primarily reflecting the cost of antiretroviral therapy) is approximately \$36,000 per QALY and that care of identified HIV-infected patients drives both cost and benefits. Compared with the costs of care, testing costs are much less important. It is often overlooked by those objecting to the cost of routine HIV testing that the real costs and the real benefits to screening accrue over time in the course of successful treatment.

Recent analysis has examined the cost-effectiveness of the entire screening process itself: offering the test, accepting the test, returning for test results, and linking to appropriate care. Walensky and colleagues defined the “index of participation” as the product of the probability of test offer and acceptance and the probability of returning for results and linkage to care (*Med Decis Making*, 2005). For example, the index of participation for a screening program with a test offer-and-accept rate of 37% and a return-and-link rate of 88% would be 33% ($0.37 \times 0.88 =$

Table 2. Cost-Effectiveness Ratios for Select HIV-Related Interventions and for HIV and Non-HIV-Related Screening Interventions

Intervention	Drug	Cost-Effectiveness Ratio (\$/QALY) ^a	Reference
HIV Interventions			
PCP/toxoplasmosis prophylaxis	TMP-SMX	\$2600	Freedberg et al, <i>JAMA</i> , 1998
Antiretroviral therapy	Zidovudine/lamivudine/efavirenz	\$13,000	Freedberg et al, <i>N Engl J Med</i> , 2001
Genotypic resistance test, at treatment failure	NA	\$17,900	Weinstein et al, <i>Ann Intern Med</i> , 2001
Genotypic resistance test, treatment-naive	NA	\$20,200	Sax et al, <i>Clin Infect Dis</i> , 2005
Inpatient HIV screening	NA	\$15,100	Walensky et al, <i>Am J Med</i> , 2005
MAC prophylaxis	Azithromycin	\$44,500	Freedberg et al, <i>JAMA</i> , 1998
HIV and Other Screening Interventions			
HIV screening every 5 years in patients at high risk	NA	\$42,200	Paltiel et al, <i>N Engl J Med</i> , 2005
Breast cancer screening: annual mammogram, 50-69 years old	NA	\$57,500	Salzmann et al, <i>Ann Intern Med</i> , 1997
Colon cancer screening: FOBT + sigmoidoscopy every 5 years, 50-85 years old	NA	\$53,600	Frazier et al, <i>JAMA</i> , 2000
Type 2 diabetes: one-time FPG, > 25 years old	NA	\$63,000	CDC, <i>JAMA</i> , 1998

CDC indicates Centers for Disease Control and Prevention; FOBT, fecal occult blood test; FPG, fasting plasma glucose; MAC, *Mycobacterium avium* complex; NA, not applicable; PCP, *Pneumocystis jirovecii* pneumonia; TMP-SMX, trimethoprim-sulfamethoxazole.

^aAll costs adjusted to 2001 US dollars. Ratios from Walensky et al, *Am J Med*, 2005.

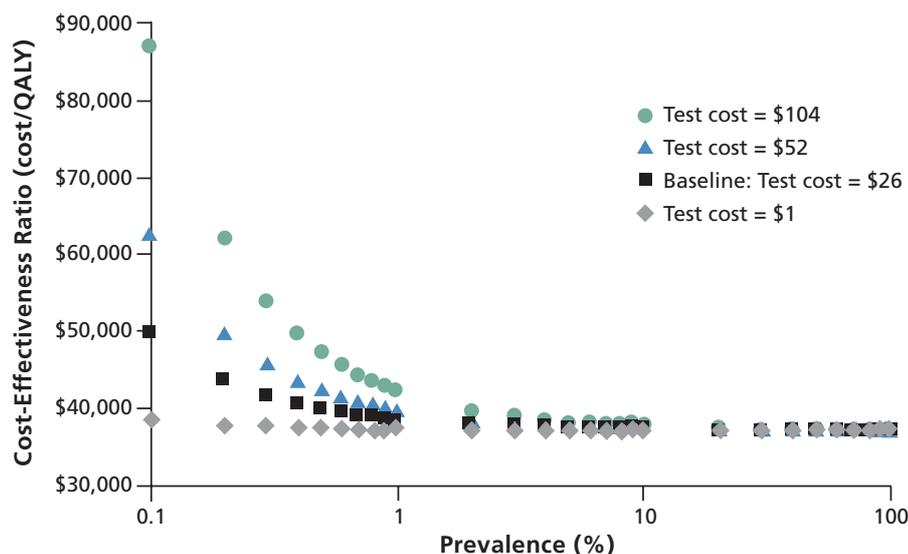


Figure 2. Cost-effectiveness ratios of HIV screening according to prevalence of undiagnosed HIV infection in the testing population and different hypothetical test costs. QALY indicates quality-adjusted life-years. Adapted from Walensky et al, *Am J Med*, 2005.

0.33); a program with an offer-and-accept rate of 88% and a return-and-link rate of 37% would have the same 33% index of participation. The authors examined the cost-effectiveness of HIV screening associated with a wide range of values for the index of participation by varying offer-and-accept and return-and-link rates from 0% to

100% in 10% intervals (undiagnosed HIV prevalence of 1%; Figure 3). The ratio for the hypothetical case of a 33% index of participation (37% offer-and-accept rate and 88% return-and-link rate) is \$38,600 per QALY; a program with only a 20% offer-and-accept rate and 20% return-and-link rate (0.04, or 4% index of participation) still has a

cost-effectiveness ratio of \$43,400 per QALY. Indeed, cost-effectiveness ratios were lower than \$50,000 per QALY for any index of participation greater than 1% (0.01).

Further investigation examined whether it is more important from a cost-effectiveness viewpoint to have higher offer-and-accept rates or higher return-and-link rates (Figure 3). Cost-effectiveness ratios were lower for index of participation values reflecting higher return-and-link rates, compared with identical indices of participation with higher offer-and-accept rates. Thus, if a choice has to be made regarding resource expenditure for a screening program, it is more cost-effective to ensure that the patient identified with a positive test result begins HIV care than to offer testing to another patient.

Conclusion

HIV simulation models are powerful tools for informing public health policy and for understanding survival, costs, and cost-effectiveness of clinical interventions. Cost-effectiveness analyses have motivated changes in policy supporting antiretroviral therapy, geno-

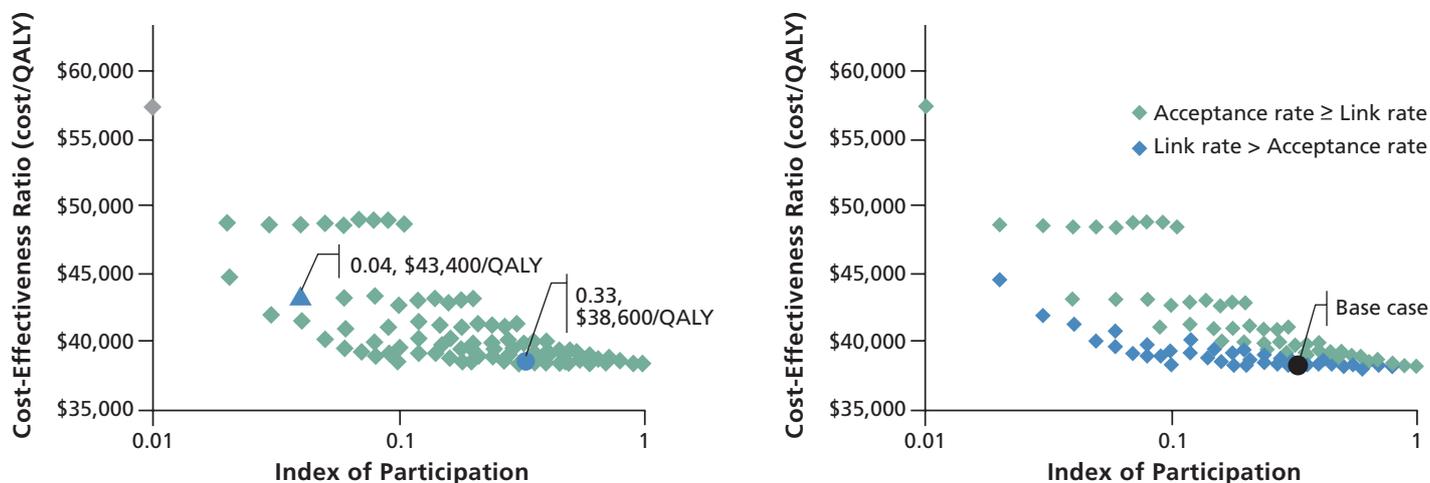


Figure 3. Left, cost-effectiveness ratios for index of participation values obtained by varying offer-and-accept rates and return-and-link rates from 0% to 100% in 10% intervals. Results assume a prevalence of undiagnosed HIV infection of 1.0%. Triangle indicates cost-effectiveness ratio associated with a 0.04 index (20% offer-and-accept rate × 20% return-and-link rate); circle, ratio for the hypothetical case of a screening program with an index of 0.33; QALY, quality-adjusted life-years. Right, same analysis with results distinguished according to whether the offer-and-accept (acceptance) rate was greater than or equal to the return-and-link (link) rate or the return-and-link rate was greater than the offer-and-accept rate. Base case indicates a hypothetical case of 0.33 index. Adapted from Walensky et al, *Med Decis Making*, 2005.

typic testing in treatment-experienced and treatment-naive patients, and expanded programs for HIV screening and linkage to care.

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

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Suggested Reading

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Correction

There was an error in a figure in the article "Occupational and Nonoccupational Postexposure Prophylaxis for HIV in 2009" (*Topics in HIV Medicine* 2009;17[3]:104-108). On page 106, the colors for the labels for the 2 drug regimens in the bottom graph of Figure 1 were inadvertently switched from the original. The figure posted on our Web site (www.iasusa.org) is correct.

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Letter

When Silence Isn't Golden

To the Editor: I had a strong response to the *Telling Stories* column by Scipio-Bannerman.¹ The author's troubling encounter with HIV patient confidentiality is reminiscent of the early years of the retroviral pandemic before the multidisciplinary approach evolved. Practitioners now collaborate with colleagues in areas of public health, psychiatry, social services, and financial assistance to address the complex spectrum of nonmedical issues that arise. This support system helps establish and preserve a trusting, long-term practitioner-patient relationship that is vital for treating the chronicity of HIV disease. Confidentiality and disclosure issues demand an ongoing dialogue, starting in the pre- and posttest counseling sessions and addressed periodically thereafter, reflecting the "expected" standard of care. The author did not comment on the patient's antiretroviral treatment history, if any, or viral load, which theoretically could compound the potential outcomes of unsafe sexual behavior, including infecting the partner and pregnancy. In modern-day medical care of HIV infection, preserving patient confidentiality and public health safety should be simultaneously obtainable goals.

I reviewed the Pennsylvania law (Act 148, Confidentiality of HIV-Related Information Act) referenced by the author. Both that law and HIPAA (Health Insurance Portability and Accountability Act) would have allowed disclosure of confidential HIV-related information in this case, so practitioners' hands are not tied nor their voices silenced by legal mandates. Instead, the author believed she could not engage her pa-

tient. It is mandatory for clinicians to establish a strong foundation of mutual trust and respect with an HIV-infected patient, allowing them to comfortably intervene in such a situation.

The extensive legislation and bureaucracy surrounding HIV-related confidentiality laws are counterproductive to clinicians' best efforts to retard the ongoing transmission of HIV and associated sexually transmitted diseases. The clinical consequences of each generation of viral mutations add to this difficult endeavor. It is time to aggressively slow down the trajectory of HIV infection and coinfections. Given current economic constraints and a decades-old pandemic, the energy and money allotted to creating and managing legislative guidelines should be reevaluated and redirected toward stopping the disease itself.

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 Palm Beach Gardens, FL

1. Scipio-Bannerman J. When silence isn't golden. *Top HIV Med.* 2009;17:13.

In Reply: I appreciate the response from Ms Pollard-Colombo. I share her vision of preserving patient confidentiality and public health safety as obtainable and simultaneous goals. In an ideal world, it would be possible, yet we work in the real world, with real people and real issues: people who (generally speaking) are not currently accessing the health care system or its support programs on a regular basis, people who are disenfranchised, powerless, and marginalized. Add the generally pervasive distrust of the medical community by this patient population

(post-Tuskegee racial discrimination), and you have my workplace reality.

Like Ms Pollard-Colombo, I, too, have been an active observer of the HIV pandemic. It also feels personal to me because I have witnessed the face of the disease change from that of primarily a white man to one that looks like mine. And though medicine has made giant leaps in addressing the needs of HIV-infected people, complicated privacy laws and the global economy have pushed us back a few yards.

In the case I described, I technically could have disclosed the young man's HIV serostatus to my patient because I obtained his status through a non-HIPAA source. But picture the tables turned! Suppose my female patient is HIV infected and engaged to be married. She informs me that she has decided not to inform her intended spouse of the infection. I question whether the HIPAA or the Pennsylvania law would allow me to disclose her status to her fiancé.

In addition to a legal dilemma, this is a moral and ethical question that lawyers may debate for years to come. For as much work as has been done to address HIV, there is much more to do on the social and medical fronts. As the saying goes, "we have miles to go before we sleep."

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