

AIDS CLINICAL CARE

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FEATURE

Top Stories of 2008

As is true every year in HIV research, 2008 brought with it both dramatic progress and some significant failures. Certainly, our therapies have grown better and better, with virologic suppression now an achievable reality for virtually all patients, regardless of baseline stage of disease or degree of drug resistance. Our attempts at prevention, however, have continued to fail, most notably in the vaccine arena, where a once-promising adenovirus-based vaccine proved ineffective and possibly harmful. These failures have forced us to completely reconsider how we should approach HIV prevention, with a greater focus on antiretroviral therapy for both those with the virus and those at risk. In the next year, we can anticipate not only the usual incremental advances in treatment but also greater progress (and challenges) as therapy is made more broadly available to the developing world.

— **Paul E. Sax, MD**

Earlier HIV Treatment Is Gaining Momentum

Evidence accumulated in 2008 to support starting ART at CD4 counts >350 cells/mm³.

Clinicians have long debated the question of when to start antiretroviral therapy (ART) in HIV-infected, asymptomatic patients. Although no definitive answer has emerged, data presented in 2008 provide support for earlier treatment initiation.

Current guidelines from the U.S. Department of Health and Human Services recommend ART for all patients who have CD4 counts <350 cells/mm³ or AIDS-associated morbidity (*AIDS Clin Care* Dec 2008, p. 101). They also

recommend ART, regardless of CD4-cell count, in three select groups of patients: HIV-infected pregnant women, patients with HIV-associated nephropathy, and patients with HIV and hepatitis B virus (HBV) coinfection in whom HBV treatment is indicated. For HIV-infected patients with CD4 counts >350 cells/mm³ who do not meet any of these criteria, the recommendation is to consider treatment on an individual basis, factoring in the patient's interest in therapy and commitment to high-level adherence. Guidelines from other organizations are similar, except that they identify additional patients for whom treatment should be considered at CD4 counts >350 cells/mm³. The International AIDS Society–USA specifically mentions patients with high viral loads (>100,000 copies/mL), rapidly declining CD4 counts (>100 cells/mm³ per year), active hepatitis C virus infection, or high cardiovascular risk (*AIDS*

Clin Care Oct 2008, p. 81, and *JAMA* 2008; 300:555). The European AIDS Clinical Society mentions those older than 55.

Recent observational data indicate that starting ART as early as these guidelines recommend — or perhaps even earlier — is likely to protect patients against both AIDS and non-AIDS events. In the FIRST study, patients who achieved higher CD4 counts on therapy (>350 cells/mm³) had lower rates of both AIDS- and non-AIDS events (*AIDS Clin Care* Jul 2008, p. 58, and *AIDS* 2008; 22:841), whereas patients without good immunologic response to therapy had increased risk for both types of events, attributable to time spent with a low CD4-cell count (*AIDS Clin Care* Oct 2008, p. 85, and *J Acquir Immune Defic Syndr* 2008; 48:541). In the DAD study, the rate of fatal non-AIDS-related malignancies was 10 times lower in patients with CD4 counts

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Only 18% of pregnant women are tested for HIV infection in low- and middle-income countries. Testing rates are even lower (8%) among infants born to HIV-positive women.

UNICEF, UNAIDS, and WHO. *Children and AIDS: Third stocktaking report, 2008.*

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>500 cells/mm³ than in those with CD4 counts <50 cells/mm³ (*AIDS Clin Care* Dec 2008, p. 100, and *AIDS* 2008; 22:2143). Finally, in the NA-ACCORD study, the risk for death during follow-up was 43% lower among patients who started ART at CD4 counts between 351 and 500 cells/mm³ than among those who started at <350 cells/mm³ (*AIDS Clin Care* Dec 2008, p. 97, and Abstract 896b, 2008 Joint ICAAC/IDSA Meeting).

This body of evidence further stimulates interest in randomized trials that compare treatment initiation at CD4 counts >500 cells/mm³ versus <350 cells/mm³. One such trial, the international START study, is modeled after the successful SMART study and will begin soon. — **Keith Henry, MD**

Abacavir Turmoil

Both the safety and efficacy of this NRTI were drawn into question in 2008.

Abacavir was approved in 1998, but 2008 was widely expected to be the drug's best year yet. Simon Mallal had recently presented data showing that HLA-B5701 testing could predict hypersensitivity reactions, the major obstacle to widespread abacavir use, with previously unimaginable accuracy (*AIDS Clin Care* Oct 2007, p. 81, and Abstract WESS101, 4th IAS Conference on HIV Pathogenesis, Treatment and Prevention, 2007). Treatment guidelines from the U.S. Department of Health and Human Services (DHHS) had elevated the fixed-dose abacavir/3TC combination to preferred status, and sales were increasing accordingly . . . and then the turmoil started.

In February 2008, investigators from the DAD study reported that recent abacavir use might double the risk for heart attack in HIV-infected people (*AIDS Clin Care* Apr 2008, p. 29, and Abstract 957c, 15th Retrovirus Conference, 2008). Additional analyses confirmed that the increased risk was limited to people who were currently using the drug or had done so in the previous 6 months (*AIDS Clin Care* May 2008, p. 37, and *Lancet* 2008; 371:1417). These findings were surprising, unexplained, and at least initially unbelievable because abacavir had always been considered to have a favorable metabolic

profile. Subsequent analyses from other studies have been conflicting. The SMART trial revealed an increase in cardiac events among patients taking abacavir that was similar to that seen in DAD (*AIDS Clin Care* Oct 2008, p. 82, and *AIDS* 2008; 22:F17), but another cohort study, HOPS, did not (Abstract THPE0236, XVII International AIDS Conference, 2008). Given that DAD and SMART are observational trials, we cannot exclude the possibility of allocation bias (i.e., that patients with cardiac risk were started on abacavir preferentially). A pooled analysis of data from 54 clinical trials conducted by the maker of abacavir showed no association between abacavir use and risk for myocardial infarction (*AIDS Clin Care* Oct 2008, p. 78, and Abstract WEAB0106, XVII International AIDS Conference, 2008); however, the follow-up in these trials, even when pooled, was much shorter than in the DAD analysis. The most critical analysis still missing from these studies is the breakdown by line of therapy (i.e., use in treatment-naïve vs. experienced patients).

The other bad news about abacavir came from the ongoing ACTG 5202 trial, which involves 1858 treatment-naïve patients who were randomized to receive abacavir/3TC or tenofovir/FTC (each together with efavirenz or boosted atazanavir). In an interim analysis, the Data and Safety Monitoring Board concluded that abacavir/3TC was significantly less effective than tenofovir/FTC in suppressing HIV in patients with high baseline viral loads (≥100,000 copies/mL; *AIDS Clin Care* Oct 2008, p. 77, and Abstract THAB0303, XVII International AIDS Conference, 2008). Grade 3 and 4 adverse events were also more common in abacavir recipients. All patients receiving abacavir/3TC who entered the trial with high viral loads have been given the opportunity to switch to different regimens. The reasons for the study findings remain unclear and will require additional analysis.

Based on this collective evidence, the DHHS opted in November to switch the status of abacavir/3TC from a preferred combination back to an alternative one, bringing the saga full circle.

— **Helmut Albrecht, MD**

Beyond Abacavir/3TC: Good News on First-Line Regimens

Positive data emerged this year to support the use of boosted atazanavir and boosted darunavir in treatment-naïve patients. Raltegravir also looks promising in this population.

Although the controversy about the safety and virologic efficacy of abacavir/3TC was probably the biggest story in first-line regimen news this year, we also heard a lot of positive data about boosted PIs and raltegravir.

Ritonavir-boosted atazanavir has long been used in treatment-naïve patients, but its safety and efficacy were only recently confirmed in the CASTLE study. At 48 weeks, ritonavir-boosted atazanavir was determined to be noninferior to lopinavir/ritonavir when each was given with tenofovir/FTC; virologic response rates (viral load <50 copies/mL) were 78% and 76%, respectively (*AIDS Clin Care* Oct 2008, p. 84, and *Lancet* 2008; 372:646). By 96 weeks, rates of virologic response favored ritonavir-boosted atazanavir (74% vs. 68%), but the difference was driven by study discontinuations rather than by rates of virologic failure, which were the same in the two arms (*AIDS Clin Care* Dec 2008, p. 98, and Abstract H-1250d, 2008 Joint ICAAC/IDSA Meeting).

Ritonavir-boosted darunavir was approved by the FDA this year for use in treatment-naïve patients (*AIDS Clin Care* Dec 2008, p. 102) and was also elevated to the status of preferred PI in the U.S. Department of Health and Human Services treatment guidelines (*AIDS Clin Care* Dec 2008, p. 101). Both decisions were based on 48-week data from the ARTEMIS study, which showed virologic response rates (viral load <50 copies/mL) of 84% in those receiving ritonavir-boosted darunavir and 78% in those receiving lopinavir/r, each with tenofovir/FTC (*AIDS Clin Care* Sep 2008, p. 70, and *AIDS* 2008; 22:1389). Response rates at 96 weeks favored boosted darunavir (79% vs. 72%), again driven at least partially by higher rates of study discontinuation in the lopinavir/r arm than in the boosted darunavir arm (23% vs. 17%), although the boosted darunavir arm did have fewer virologic failures (*AIDS Clin Care*

Dec 2008, p. 98, and Abstract H-1250c, 2008 Joint ICAAC/IDSA Meeting).

The new integrase inhibitor raltegravir is not yet approved for use in treatment-naïve patients, but studies in this population have been very encouraging. A previously presented dose-ranging study of raltegravir with tenofovir/3TC demonstrated excellent virologic responses in all dose arms. After 48 weeks, all participants received 400 mg of raltegravir twice daily. At week 96, in an intent-to-treat, missing-equals-failure analysis, 83% of raltegravir recipients had viral loads <50 copies/mL (*AIDS Clin Care* Oct 2008, p. 78, and Abstract TUAB0102, XVII International AIDS Conference, 2008). A larger phase III study showed raltegravir to be non-inferior to efavirenz in first-line regimens that also contained tenofovir/FTC (*AIDS Clin Care* Dec 2008, p. 97, and Abstract H-896a, 2008 Joint ICAAC/IDSA Meeting). At 48 weeks, virologic response rates (viral load <50 copies/mL) were 86% in the raltegravir arm and 82% in the efavirenz arm. The raltegravir arm had significantly shorter times to virologic response; significantly greater increases in CD4 counts (mean, 189 vs. 163 cells/mm³); and significantly lower rates of clinical adverse events overall, drug-related clinical adverse events, and early central nervous system events.

Taken together, these data illustrate the range of options available for contemporary management of HIV infection. HIV-infected patients and their clinicians share a much improved treatment outlook as 2008 comes to a close.
— **Charles B. Hicks, MD**

Newer Drugs Strikingly Effective When Given Together

Regimens that contain at least two of four recently approved drugs — darunavir, maraviroc, raltegravir, and etravirine — have yielded spectacular results in uncontrolled studies.

The quartet of recent drug approvals that began with darunavir in 2006 and was followed by maraviroc and raltegravir in 2007 and then etravirine this year (*AIDS Clin Care* Mar 2008, p. 17) has completely transformed the

management of treatment-experienced patients. These drugs all demonstrated impressive rates of virologic suppression in the pivotal studies that led to their approvals — specifically, the POWER (darunavir), MOTIVATE (maraviroc), BENCHMRK (raltegravir), and DUET (etravirine) studies.

Of course, research does not always translate into practice, but, in this instance, the reality has been better than the controlled trials: In a single-arm study from France, 90% of 103 highly treatment-experienced patients who received darunavir, raltegravir, and etravirine achieved viral loads <50 copies/mL by week 24 (Abstract THAB0406, XVII International AIDS Conference, 2008). Similarly, 50 of 53 patients co-enrolled in the Kaiser expanded-access programs for etravirine and raltegravir achieved virologic suppression by 24 weeks (Abstract H-1263, 2008 Joint ICAAC/IDSA Meeting).

One possible explanation for the staggering success rates in these studies is that clinicians can now prescribe at least two — and often three — fully active agents, whereas in the clinical trials, the study protocol sometimes limited the use of investigational drugs (e.g., in the MOTIVATE studies of maraviroc, use of darunavir, raltegravir, and etravirine were prohibited). With this degree of treatment success, the number of patients with highly resistant virus who cannot be treated successfully has diminished drastically (Abstract 895, 15th Retrovirus Conference, 2008), a state of affairs that was hardly imaginable just 3 years ago.

If a downside to this progress exists, it is the relative lack of promising antiretrovirals in the pipeline, especially those that target multiply resistant virus. For example, the maturation inhibitor bevirimat appears to be active in only a subset of individuals, specifically the 60% or so who lack a key polymorphism in the Gag region of HIV (*AIDS Clin Care* Dec 2008, p. 104, and Abstract H-891, 2008 Joint ICAAC/IDSA Meeting) — very disappointing news for those awaiting a treatment option for patients with resistance to these newer agents.

— **Paul E. Sax, MD**

Crash and Burn of HIV Vaccine Candidates

The focus of HIV vaccine research was redefined in 2008.

The HIV vaccine world has been in turmoil ever since the fall of 2007, when Step Study investigators first reported the unexpected failure of the Merck adenovirus serotype 5 (Ad5) HIV vaccine (*AIDS Clin Care* Nov 2007, p. 93). Although the lack of protection offered by this vaccine was certainly disappointing, the larger, more perplexing issue has been the increase in risk seen among vaccine recipients who were both Ad5-seropositive and uncircumcised (see page 7). Detailed analyses from the trial have yielded some clues about the failure of the vaccine — for example, we now know that only one third of vaccinees mounted both CD4 and CD8 HIV-specific T-cell responses following vaccination — but we might never have a complete explanation for the findings.

Overall, the Step Study experience has led to a major rethinking of the strategy that is being followed in the search for an HIV vaccine (*Science* 2008; 321:530). Earlier this year, the NIH convened a summit of HIV vaccine experts to discuss how best to reinvigorate and advance vaccine discovery research at this critical juncture. Soon thereafter, NIH officials cancelled a major trial (PAVE 100; *AIDS Clin Care* Sep 2008, p. 69), reflecting a conscious decision on their part to shift the focus of HIV vaccine research from product evaluation toward vaccine discovery. At the same time, researchers are debating many critical issues: Are nonhuman primates the best models in which to test for immunogenicity? Do T-cell vaccines still have a role? Are vaccines that use adenovirus vectors still viable? What can we learn from innate immunity, long-term non-progressors, and elite controllers that will guide the search for an HIV vaccine?

Until some of these questions are answered, the world of HIV vaccines will remain in turmoil, and any large phase IIB or III clinical trials will be on hold. Nevertheless, I am convinced that we will come out of this setback stronger and more knowledgeable, as some of the best and brightest minds are still working hard to develop an effective HIV vaccine — a task that has undoubtedly proven much more difficult than we had ever imagined.

— **Carlos del Rio, MD**

No Good News Yet on Anti-HIV Microbicides

Two intravaginal microbicide gels were found to be safe but ineffective.

Despite their initial promise, topical microbicides have yet to prove effective for HIV prevention. This year, two intravaginal gels — cellulose sulfate and Carraguard — were officially added to the list of failed compounds.

Cellulose sulfate was tested in a phase III, randomized, placebo-controlled trial among nearly 1400 women in Africa and India. The trial was halted in early 2007 after preliminary results suggested that cellulose sulfate might enhance HIV acquisition (*AIDS Clin Care* Mar 2007, p. 27). In the final analysis, however, infection rates did not differ significantly between the cellulose-sulfate and placebo groups (*AIDS Clin Care* Sep 2008, p. 71, and *N Engl J Med* 2008; 359:463). Subsequent in vitro studies of cellulose sulfate revealed that this compound inhibits HIV infection when used at high concentrations but facilitates infection when used at low concentrations (*AIDS Res Human Retroviruses* 2008; 24:925).

Carraguard gel was tested in a phase III, randomized, placebo-controlled trial involving more than 6000 women in South Africa. The compound was well tolerated but did not reduce the likelihood of HIV acquisition (*Lancet* 2008; 372:1977). Potential reasons for the failure of these microbicides include inflammatory reactions, alterations in the normal vaginal flora following cumulative use of the gels, and, possibly, localized immune dysfunction.

The use of antiretrovirals as microbicides is now an active area of research. One-percent tenofovir gel has yielded promising results in animal studies (*PLoS Med* 2008; 5:e157) and is currently being tested in a large clinical trial among high-risk women in South Africa. However, the potential for HIV resistance after topical application of antiretrovirals is a real concern, and the implications for future systemic therapy must be considered. Condom use and HIV/STD counseling must continue to be major components of all future trials. In addition, preclinical, phase I, and phase II studies must rigorously evaluate the local effects of microbicides on epithelial tissues. — **Sonia Nagy Chimienti, MD**

HIV Incidence in the U.S.: New Methods Result in a Higher Estimate

Overall, the number of new infections in the U.S. is holding steady but is higher than we originally thought.

For nearly 20 years, the news about HIV incidence in the U.S. has been the same: The CDC has consistently reported that about 40,000 new HIV infections occur each year, mostly in men who have sex with men (MSM) and at higher rates among blacks and Hispanics than among whites. This year, part of that story changed dramatically, and part remained the same. In any case, the news was rarely good.

For the first time, CDC officials were able to directly measure the rate of new infections in parts of the U.S., using assays that differentiate recent infections from long-standing ones. They then employed a host of complicated statistical methods to estimate incidence for the entire country. What they found is that the number of new infections has indeed been holding steady, at least since around 2000, but is much higher than previously suspected — about 56,000 cases per year rather than 40,000 (*AIDS Clin Care* Oct 2008, p. 86, and *JAMA* 2008; 300:520). The CDC has stated explicitly that this new estimate does not reflect an increase in incidence but rather use of new laboratory and statistical methods. More than half the new cases continue to occur in MSM, and two thirds are in individuals younger than 40. Racial/ethnic disparities persist, with HIV diagnosed in blacks at a rate about seven times that of whites and three times that of Hispanics.

Although HIV incidence has remained stable in the population as a whole, it has changed considerably within various subgroups. From 2001 through 2006, the number of new diagnoses decreased among most transmission groups (by 4.4% among heterosexuals and by 9.5% among injection-drug users) but crept upward among MSM by about 1.5% per year (*MMWR Morb Mortal Wkly Rep* 2008; 57:681). Infections in this group seem to be occurring primarily in young men of color (age range, 13–29), with the number of new cases in blacks outstripping that in Hispanics (*MMWR Morb Mortal Wkly Rep* 2008; 57:985). From 2001 through 2006, the number of new cases in black MSM aged 13 to

24 nearly doubled. These shocking trends are a reflection of our failure to influence behavior change and HIV testing rates in this group. Reaching young MSM, particularly those from minority racial/ethnic groups, is now a key priority for testing and prevention efforts. — **Judith Feinberg, MD**

Antiretroviral Rollout — Successes and Challenges

The continued success of ART rollout programs will depend on efforts to prevent resistance and ensure adequate follow-up.

The rollout of antiretroviral therapy (ART) in resource-limited settings has been a stunning success, with more than 3 million adults and children initiating ART in the past 4 years. Two thirds of these individuals are in sub-Saharan Africa, the most under-resourced area in the world. Although initial skepticism about infrastructure and medication adherence has abated somewhat, new (but not unexpected) concerns have arisen.

One set of concerns is specific to the most frequently used initial regimen worldwide — d4T + 3TC + efavirenz or nevirapine. Although this combination is potent, easily administered, and relatively inexpensive, it carries the risk of substantial cumulative toxicity. Furthermore, because 3TC and the NNRTIs have low genetic barriers to resistance, the regimen is associated with selection of resistance mutations and subsequent therapeutic failure. This shortcoming is made worse in resource-limited settings, where the use of clinical or CD4-cell-count criteria rather than viral-load monitoring results in late recognition of treatment failure, and the boosted PIs necessary for second-line regimens are prohibitively expensive and limited in availability. At several meetings this year, researchers described antiretroviral resistance in Africa and Asia (Abstracts MOPDA204 and LBPE1131, XVII International AIDS Conference, 2008; Abstract O113, 9th International Congress on Drug Therapy in HIV Infection, 2008; and Abstract 796, 2008 HIV Implementers' Meeting). What is particularly disturbing is that about 5% of patients initiating ART in some of these regions had primary resistance, most likely acquired through high-risk sexual

or drug-use behavior with patients who had resistant virus.

Another worrisome development in many antiretroviral programs is substantial loss to follow-up. Such loss is not unexpected, given the limited resources available to continue prioritizing enrollment and initiation of ART for the millions of patients who still require it while also providing long-term follow-up care for those already in treatment. Although precise outcomes are generally not known for patients lost to follow-up, suspicion is increasing that many of these patients are dying prematurely (*Bull World Health Organ* 2008; 86:559, *PLoS Med* 2007; 4:e298, and *J Acquir Immune Defic Syndr* 2008; 47:101).

The extraordinary success of ART rollout will continue to expand, but the issues described here must be addressed now to maximize benefit. Potential solutions include (1) reducing the cost and increasing the availability of nonthymidine analogues (tenofovir and abacavir) so that they can be used in place of d4T and AZT in initial regimens, (2) reducing the cost and increasing the availability of boosted PIs, (3) reducing the cost of viral-load monitoring and resistance testing while developing new technologies appropriate for resource-constrained environments, and (4) training and deploying much larger numbers of community workers to support and follow-up on patients receiving ART.

— **Gerald H. Friedland, MD**

Rapid HIV Testing Is Not Without Its Flaws

The low specificity of the oral swab tests remains a concern, as do poor follow-up rates among those testing positive.

Policy statements calling for expanded HIV testing in the U.S. rely heavily on OraSure rapid saliva and blood testing because the standard two-visit ELISA/Western blot sequence is considered too cumbersome for most settings. However, point-of-care rapid testing has accuracy problems and may also have follow-up problems, as several studies made clear this year.

A large study of an opt-out approach to HIV screening in a Washington DC emergency department (ED) found 26 of 2486 (1%) patients reactive on oral

swab testing (*AIDS Clin Care* Feb 2008, p. 13, and *J Acquir Immune Defic Syndr* 2007; 46:395). However, only 13 (50%) of those patients returned to the hospital or a local free clinic for confirmatory testing. Nine had reactive Western blots, and four were confirmed to have false-positive results, for an overall specificity of 99.8% in this high-prevalence area.

The test did not perform as well in a low-prevalence area. In a Boston ED, 39 (5%) of 849 patients tested with oral swabs had reactive tests; of the 31 who had confirmatory testing, only 5 were confirmed to be HIV-infected, for a specificity of 96.9% (*AIDS Clin Care* Oct 2008, p. 82, and *Ann Intern Med* 2008; 149:153). This value is significantly lower than both the manufacturer's published results and the 98% minimum specificity required by the FDA for rapid HIV tests.

A surge in false-positive results from oral swab tests was noted in New York City's public health clinics between November 2007 and April 2008. The nadir of specificity during those months was 98.9%. Although the test's performance subsequently improved, clinic workers in this high-prevalence area "expressed a lack of confidence" in the oral swab test, and the clinics now use rapid whole-blood fingerstick testing instead (*AIDS Clin Care* Sep 2008, p. 70, and *MMWR Morb Mortal Wkly Rep* 2008; 57:660).

Meanwhile, the sensitivity of rapid testing might also be occasionally flawed. A 28-year-old man with oral thrush repeatedly tested negative with oral swabs in a Michigan ED. He was subsequently found to have late-stage AIDS and only a very faint gp41 band on Western blot testing — gp41 is the only band assayed by the rapid test (*AIDS Clin Care* Sep 2008, p. 71, and *Ann Intern Med* 2008; 149:71).

Rapid testing is the way of the future, but the problem of false-positive results, especially in low-prevalence areas, remains a concern. As the tests are more widely deployed in these areas, algorithms must be fine-tuned to minimize the anxiety that false-positive results cause. As for higher-prevalence settings, the emphasis must be on maximizing follow-up for confirmatory testing.

— **Abigail Zuger, MD**

The Prospect of PrEP

The use of antiretrovirals for preexposure prophylaxis is being widely investigated. What if it's found to be safe and effective?

Twenty-five years into the HIV/AIDS epidemic, the search for safe and effective HIV prevention methods continues. Much hope now rests on antiretrovirals for preexposure prophylaxis (PrEP). Several clinical trials are currently under way to assess the efficacy of this intervention: a CDC study investi-

gating oral tenofovir among intravenous-drug users in Thailand, a USAID-funded study of 1% tenofovir gel among high-risk women in South Africa, and three trials of coformulated oral tenofovir/FTC (Truvada) — a CDC study among high-risk men and women in Botswana; a Gates Foundation-funded study among serodiscordant heterosexual couples in Kenya and Uganda; and an NIH-funded study among men who have sex with men in South Africa, Peru, Ecuador, Brazil, and the U.S.

In addition, at least two other PrEP trials are expected to start in 2009. If results from these trials demonstrate effectiveness, we can expect immense pressure to implement PrEP immediately on a widespread scale. However, several important issues must be considered first.

Tolerance and Adherence: The side effects of antiretrovirals might not be tolerated as readily by healthy asymptomatic individuals receiving PrEP as they are by individuals taking the drugs for therapeutic reasons. This lack of tolerance could compromise adherence, potentially leading to suboptimal protection and, in some circumstances, to drug resistance.

HIV Drug Resistance: Obviously, resistance cannot occur in uninfected individuals, but it might develop in those who become infected while taking PrEP. Whether this would compromise their future HIV treatment options remains unknown. An additional concern is whether using the same drugs for therapy and prevention will fuel resistance.

Risk Behavior: People might stop using proven interventions such as condoms if a new intervention such as PrEP becomes available — even if the new intervention is less effective.

Cost: PrEP programs are likely to be expensive, not only because of drug costs but also because of programmatic and laboratory monitoring costs, including regular HIV testing in PrEP recipients.

Clearly, if PrEP is shown to be safe and effective, implementation programs will require substantial resources with extensive community education about the indications, availability, and effectiveness of the intervention and the need for concomitant use of other proven prevention strategies. Serious consideration should be given to reserving an entire class of antiretrovirals (or more) solely for prevention. Finally, long-term follow-up and surveillance will be necessary to monitor behavior changes, adverse events, adherence levels, drug resistance patterns, and the effect of drug resistance on later AIDS treatment.

— **Salim S. Abdool Karim, MD, PhD**

NEWS IN CONTEXT

Which ART Regimen Is Best After Receipt of Single-Dose Nevirapine?

Preliminary results from the OCTANE trial suggest that lopinavir/r-based regimens are more effective than nevirapine-based ones, particularly when ART is initiated shortly after exposure to single-dose nevirapine.

Women who receive single-dose nevirapine during labor may be better off with subsequent antiretroviral therapy (ART) regimens that contain lopinavir/ritonavir rather than nevirapine, according to a recent press release from the National Institute of Allergy and Infectious Diseases. This finding arose during a recent interim analysis of the phase III OCTANE trial, which is taking place in seven African countries. Nevirapine is widely used throughout the developing world for both treatment of HIV infection and prevention of mother-to-child HIV transmission.

A total of 243 HIV-infected women in the OCTANE trial who had previously received single-dose nevirapine were randomized to receive FTC/tenofovir plus either nevirapine or lopinavir/r. The primary outcome was a composite of death or virologic failure, with the latter defined as a <10-fold reduction in viral load by week 12 or a viral-load measurement ≥ 400 copies/mL at or after week 24.

During a median follow-up of 66 weeks, 24% of women in the nevirapine group died or experienced virologic failure, compared with only 7% in the lopinavir/r group. The difference between treatment groups was particularly striking (38% vs. 0%) among women who had evidence of nevirapine resistance at baseline. (Resistance testing was done retrospectively, and results were not available in real time.) However, on a more positive note, the two regimens appeared to be comparable in the small group of women who deferred ART initiation until at least 2 years after delivery. The proportion of these women who died or experienced virologic failure was 8% in the nevirapine group and 10% in the lopinavir/r group.

Per the Data and Safety Monitoring Board, study participants are being informed of these preliminary results and counseled to talk to their clinicians about how to proceed. Lopinavir/r is being made available to those in the nevirapine group who choose to switch therapy. Baseline resistance results are also now available and being shared with participants. Follow-up of all participants will continue as planned, until June 2009. A concurrent OCTANE trial, comparing the same two regimens among 502 women who have never taken single-dose nevirapine, will also continue as planned. These results are being submitted for possible presentation at the upcoming Retrovirus Conference in Montreal.

— **Catherine Tomeo Ryan**

DSMB finds ritonavir-boosted lopinavir superior to nevirapine in HIV-positive women who previously took single-dose nevirapine [press release]. Bethesda, MD: National Institute of Allergy and Infectious Diseases; Oct 28, 2008.

JOURNAL WATCH HIV

A Pivotal Step for HIV Vaccines

Investigators continue to explore why the HIV vaccine used in the Step Study failed to protect high-risk individuals from HIV acquisition — and seemed to increase risk in some.

The development of an effective HIV vaccine was thrown a complex and disheartening curve in late 2007 when investigators halted a large phase IIB clinical trial of a vaccine designed to elicit cell-mediated immune responses to HIV (*AIDS Clin Care* Nov 2007, p. 93). The much-discussed results of this trial (called the Step Study) have now been published with expanded analyses, including immunologic findings.

The trial involved 3000 men and women at high risk for HIV acquisition who were randomized to receive either placebo or a vaccine composed of three recombinant adenovirus serotype 5 (Ad5) vectors containing *gag*, *pol*, and *nef* genes derived from clade B HIV-1. Approximately 38% of study participants were women, and more than 96% of the men reported sex with men. The trial took place in North and South America, the Caribbean, and Australia and was cosponsored by the vaccine manufacturer (Merck) and the HIV Vaccine Trials Network.

After 33 months, a prespecified interim analysis was conducted among the 1500 participants with low preexisting immunity to Ad5. No benefit was found among vaccine recipients, in terms of either HIV acquisition rates or mean HIV viral load. Given that only one HIV infection occurred in women, subsequent, detailed analyses were limited to men. These analyses showed that, among men with preexisting immunity to Ad5, vaccine recipients had significantly higher rates of HIV acquisition than did placebo recipients (5.1% vs. 2.3% per year). In post hoc analyses, this increased risk among vaccine recipients was most pronounced in men who were both uncircumcised and Ad5-seropositive (hazard ratio, 3.9), but it was also seen in men who were one or the other. These findings were not confounded by common demographic and HIV risk variables, although some important potential confounders — such as herpes simplex virus type 2 serostatus and human

leukocyte antigen type — are still under analysis. The authors hypothesize that the mechanism for enhanced HIV acquisition might be related to mucosal immune responses in people with previous exposure to Ad5.

Immunologic analyses confirmed that the vaccine was highly immunogenic. However, cellular immune responses to the vaccine did not explain clearly the lack of efficacy or the suggestion of enhanced risk in certain subgroups.

Comment: The Step Study findings are pivotal for the HIV vaccine field. A sister trial evaluating the same vaccine in South Africa was also stopped early, and the NIH decided to cancel a planned efficacy trial of a different Ad5 vaccine (*AIDS Clin Care* Sep 2008, p. 69). The results suggest that T-cell responses of the quality, magnitude, and breadth induced by the current batch of viral vector vaccine candidates will not alone be sufficient to modify disease progression. Instead, vaccines are needed that induce neutralizing antibody to HIV, either alone or in combination with cellular responses. Although the analyses showing enhanced HIV acquisition in some groups were post hoc and should be viewed with caution, these data make the previously hypothetical risk of increased HIV acquisition among vaccine recipients an important issue to be addressed in future vaccine development.

Despite the widespread use of the term “failure” in the media, the trial itself was an enormous success — with a definitive answer achieved in 33 months, high levels of protocol adherence, and rapid unblinding once the results were known. — **Frances Priddy, MD, MPH**

Dr. Priddy is Director, Medical Affairs for the International AIDS Vaccine Initiative. She was previously an investigator for Merck-sponsored trials and was briefly the Principal Investigator of the Step Study at Emory University but had no role in the analyses reported here.

*Buchbinder SP et al. Efficacy assessment of a cell-mediated immunity HIV-1 vaccine (the Step Study): A double-blind, randomised, placebo-controlled, test-of-concept trial. **Lancet** 2008 Nov 29/Dec 5; 372:1881.*

*McElrath MJ et al. HIV-1 vaccine-induced immunity in the test-of-concept Step Study: A case-cohort analysis. **Lancet** 2008 Nov 29/Dec 5; 372:1894.*

Reduced Mortality Among HIV-Infected Infants

ART initiated soon after birth reduces HIV disease progression by 75% and early mortality by 76%.

Despite the success of antiretroviral prophylaxis in preventing mother-to-child HIV transmission, many infants still die from HIV-related causes in countries where seroprevalence of the virus is high. To determine whether initiating antiretroviral therapy (ART) soon after birth might slow disease progression and reduce early mortality in infants with in utero or intrapartum HIV infection, investigators conducted a phase III, randomized, open-label trial at two centers in South Africa. The results were first presented in 2007 (*AIDS Clin Care* Oct 2007, p. 82, and Abstract WESS103, 4th IAS Conference on HIV Pathogenesis, Treatment and Prevention, 2007) and have now been published.

A total of 377 HIV-infected 6- to 12-week-old infants were enrolled; all had CD4-cell percentages $\geq 25\%$. They were randomly assigned to one of three treatment strategies: early ART (generally lopinavir/ritonavir, AZT, and 3TC; initiated immediately) for either 40 weeks or 96 weeks, or deferred therapy (initiation determined by CD4-cell percentage or clinical criteria). After randomization, the infants were seen every 4 weeks until week 24, then every 8 weeks until week 48, and then every 12 weeks.

Disease progression to CDC stage C or severe stage B occurred in only 6.3% of infants in the early-therapy groups combined, compared with 25.6% of those in the delayed-therapy group (hazard ratio, 0.25; 95% confidence interval, 0.15–0.41). Mortality was also markedly lower in the early-therapy groups than in the delayed-therapy group (4.0% vs. 16.0%; HR, 0.24; 95% CI, 0.11–0.51).

Comment: Differences in disease progression and in mortality between the combined early-therapy groups and the delayed-therapy group were striking and prompted intervention by the Data and Safety Monitoring Board, even though accrual had been completed by the time these differences were demonstrated. Consequently, the deferred-therapy group was modified; infants in this group were all evaluated for possible initiation of ART.

Early diagnosis in HIV-exposed infants and prompt ART initiation (regardless of CD4-cell percentage or count) should be adopted, as recommended in the latest U.S. Department of Health and Human Services guidelines.

— **Larry M. Baddour, MD**

Dr. Baddour is Professor of Medicine in the Division of Infectious Diseases at Mayo Clinic College of Medicine, Rochester, Minnesota.

Violari A et al. Early antiretroviral therapy and mortality among HIV-infected infants. N Engl J Med 2008 Nov 20; 359:2233.

Cost-Effectiveness of Monitoring and Treatment Strategies in Resource-Limited Settings

Mathematical modeling suggests that both lives and money can be saved by monitoring CD4-cell counts regularly and starting antiretroviral therapy earlier.

In resource-limited settings, providers often make decisions about starting and switching antiretroviral regimens without the benefit of CD4-cell-count or viral-load information. Some experts argue that such imperfect decision making limits the effectiveness of individual patients' regimens and that laboratory monitoring should be implemented on a population level. Others argue, however, that laboratory monitoring would be too expensive and that resources are better spent placing additional patients on antiretroviral therapy (ART). A new cost-effectiveness analysis adds insight to the debate.

Using a mathematical model of HIV disease in South Africa, investigators examined the outcomes and costs associated with 10 different strategies for deciding when to start or switch antiretroviral regimens among patients in southern Africa. Two of the strategies involved monitoring symptoms only, four involved monitoring CD4-cell counts only, and four involved monitoring both CD4-cell counts and viral loads.

All the strategies that involved CD4-cell-count monitoring alone were associated with longer life expectancy (by 6.5 to 12.1 months) and lower costs than were the symptom-based strategies. Furthermore, the strategies that involved

starting ART at CD4 counts <350 cells/mm³ led to longer life expectancy and lower costs than did the strategies that involved waiting until CD4 counts fell below 200 cells/mm³ (the current standard of care in Africa). Although CD4-cell-count monitoring and early ART resulted in higher testing and treatment costs, these expenses were more than offset by the savings generated by avoiding hospitalizations for opportunistic diseases. Adding viral-load testing extended life expectancy by about 1.8 months but also increased the cost-effectiveness ratio to \$5414 (in 2007 U.S. dollars) per life-year gained. Monitoring CD4-cell counts every 3 months was not as cost-effective as doing so every 6 months.

Comment: This sophisticated mathematical model provides cost-effectiveness data otherwise difficult to obtain without a lengthy randomized clinical trial. The findings have two important implications for current international debate: First, focusing exclusively on expanding the number of patients on ART might be shortsighted. Although appropriate monitoring has up-front costs, it might ultimately prove to be both life-saving and cost-saving. Indeed, CD4-cell-count monitoring could allow African nations to place more people on ART than they could with a seemingly less-expensive symptom-based strategy (because of the money saved by avoiding hospitalizations for opportunistic diseases). Second, starting ART earlier than is currently recommended by the WHO (i.e., at CD4 counts <350 cells/mm³ instead of <200 cells/mm³) also might save both lives and money and is probably an appropriate strategy in resource-limited settings.

— **Benjamin P. Linas, MD, MPH, and Rochelle P. Walensky, MD, MPH**

Dr. Linas is Instructor in Medicine at Harvard Medical School and an Infectious Disease Specialist at Massachusetts General Hospital in Boston. Dr. Walensky is Associate Director of the Program in Epidemiology and Outcomes Research at the Center for AIDS Research at Harvard Medical School and an Infectious Disease Specialist at Massachusetts General Hospital and Brigham and Women's Hospital in Boston.

Bendavid E et al. Cost-effectiveness of HIV monitoring strategies in resource-limited settings: A southern African analysis.

Arch Intern Med 2008 Sep 22; 168:1910.

Pneumonia Risk Still Elevated in HIV Patients

In a population-based study, the incidence of pneumonia was substantially increased in HIV-infected individuals, even those who were receiving ART and had near-normal CD4-cell counts.

The decline in opportunistic infections since the introduction of potent antiretroviral therapy (ART) has been so dramatic that infectious-complication rates are often assumed to be similar between HIV-negative and HIV-positive individuals, provided that the latter are effectively treated and have normal or near-normal CD4-cell counts. However, a recent study from Denmark challenges this assumption.

Investigators compared rates of first pneumonia-related hospitalization between 3516 HIV-infected people in the Danish HIV Cohort Study and 328,738 population-based controls (matched for sex, age, and municipality). Hospitalizations due to *Pneumocystis jirovecii* pneumonia were excluded from analysis. The study period, from 1995 through 2007, was divided into 2-year intervals.

Among HIV-positive people, the incidence of first pneumonia-related hospitalization was 50.6 per 1000 person-years at the beginning of the study, but then it declined substantially and remained stable at approximately 20 per 1000 person-years. Despite this decrease, HIV-positive people were still about 10 times more likely than HIV-negative controls to be hospitalized with pneumonia between 1997 and 2007. This increased risk was observed even among HIV-positive people with CD4 counts >500 cells/mm³ (incidence rate ratio in 2005–2007, 5.9). Injection-drug use, lower CD4-cell count, older age, and lack of ART were all predictive of pneumonia among HIV-positive patients; nadir CD4-cell count was also predictive among those not on ART.

Comment: Strengths of this study include the large sample size, the inclusive nature of the Danish HIV Cohort, the availability of complete hospitalization records, and the electronic collection of data on viral load, CD4-cell count, and ART receipt. As the authors acknowledge, the most important missing information is smoking status, because smoking rates are known to be higher among HIV-positive people than among HIV-negative ones. Still, that the

rate of pneumonia is nearly six times higher in HIV-positive people with CD4 counts >500 cells/mm³ than in HIV-negative controls serves as a reminder that ART only partially reverses the immunosuppression caused by HIV.

— **Paul E. Sax, MD**

Sogaard OS et al. Hospitalization for pneumonia among individuals with and without HIV infection, 1995–2007: A Danish population-based, nationwide cohort study. *Clin Infect Dis* 2008 Nov 15; 47:1345.

Cardiovascular Biomarkers and All-Cause Mortality in HIV-Infected Patients

High levels of hsCRP and D-dimer were associated with mortality risk in the SMART study. Patients who interrupted antiretroviral therapy experienced immediate increases in biomarker levels that were related to increases in viral load.

Previous studies have suggested that HIV-positive patients have higher levels of some inflammatory and coagulation markers than do HIV-negative patients — a finding that could at least partially explain the higher rates of non-AIDS-related morbidity and mortality observed among HIV-positive patients. However, no prospective data have been available to elucidate an association between such biomarkers and all-cause mortality in HIV-positive patients. To fill this gap, investigators conducted two substudies within the SMART trial, looking at high-sensitivity C-reactive protein (hsCRP), interleukin (IL)-6, amyloid A, amyloid P, D-dimer, and prothrombin fragment 1+2.

In the first substudy, the researchers assessed baseline biomarker levels and subsequent mortality risk using data from the 85 patients who died during the study and 170 matched controls. They found that higher baseline levels of hsCRP, IL-6, and D-dimer were significantly associated with greater all-cause mortality during the study period.

In the second substudy, the investigators tested the hypothesis that increased viral loads after treatment interruption induce activation of tissue factor pathways, thrombosis, and fibrinolysis. They evaluated biomarker levels

at baseline and 1 month later among 249 patients randomized to intermittent treatment and 250 randomized to continuous treatment. At 1 month, IL-6 and D-dimer levels were found to have increased from baseline by 30% and 16%, respectively, in the intermittent-treatment group, compared with 0% and 5%, respectively, in the continuous-treatment group. These biomarker increases in the intermittent-treatment group were significantly related to increased viral loads. The authors concluded that stopping antiretroviral therapy might increase mortality risk through mechanisms related to increased IL-6 and D-dimer levels and that researchers should study anti-inflammatory therapies to address such increases.

Comment: These substudies were relatively underpowered because of

cost constraints, the small number of deaths in the continuous-treatment arm, and other factors. Furthermore, in the first analysis, the cases and controls differed in age, CD4-cell count, coinfection with hepatitis B or C virus, smoking status, diabetes, use of blood pressure medication, and prior cardiovascular disease — all of which could have influenced interpretation of the biomarker data. Despite these limitations, the results do provide novel, provocative insights into how HIV infection and antiretroviral therapy affect an individual's health.

— **Keith Henry, MD**

Kuller LH et al. Inflammatory and coagulation biomarkers and mortality in patients with HIV infection. *PLoS Med* 2008 Oct 21; 5:e203.

GUIDELINE WATCH

Another Call for Routine HIV Screening

The American College of Physicians adds its support to a policy of HIV testing for all adolescents and adults, regardless of perceived risk.

Currently, the two most prominent sets of guidelines for HIV testing differ on target populations for routine screening: The U.S. Preventive Services Task Force calls for screening at-risk populations and neither recommends nor argues against screening other individuals. In contrast, the CDC calls for screening all adolescents and adults except in communities of exceedingly low prevalence. The influential American College of Physicians (ACP) has now endorsed a policy of broad screening as well. Among the considerations cited in support of its decision were the following:

- 10% to 25% of people who test HIV-positive report no high-risk behaviors.
- Almost half of all newly diagnosed patients are identified late in their illness, when they might not reap full benefit from antiretroviral treatment.
- People unaware of their infection status transmit an estimated 20,000 or more infections per year.
- Strong evidence indicates that, because of this ongoing transmission, screening is cost-effective even in low-risk communities.

Comment: These guidelines mark one more step toward what seems the inevitable endpoint: universal HIV screening. Of note, all guidelines still leave many details to the individual practitioner's judgment, including optimal frequency of testing in both high- and low-risk individuals. However, the ACP has provided one helpful tip for practitioners in low-risk communities: If 4000 consecutive, routine HIV tests are negative, your community prevalence is probably $<0.1\%$, and you are justified in reassessing the need for further testing of low-risk individuals.

— **Abigail Zuger, MD**

Qaseem A et al. Screening for HIV in health care settings: A guidance statement from the American College of Physicians and HIV Medicine Association. *Ann Intern Med* 2009 Jan 20; [e-pub ahead of print].

CD4-Cell Recovery — Does the Regimen Matter?

Perhaps not, but the details of this study make its relevance in many practice settings uncertain.

Some experts argue that PI-based antiretroviral regimens lead to greater CD4-cell increases than do other combinations. Support for this argument comes in part from ACTG 5142, in which patients treated with lopinavir/ritonavir gained significantly more CD4 cells during a 48-week period than did those treated with efavirenz, even though the efavirenz group had a higher rate of virologic response (*AIDS Clin Care* Jul 2008, p. 59 and *N Engl J Med* 2008; 358:2095). Now, investigators have evaluated this issue among 3293 patients in the Swiss HIV Cohort Study. All the patients initiated their first combination regimens between 1996 and mid-2007. Most such regimens included unboosted PIs (78.7%) rather than NNRTIs (13.7%) or ritonavir-boosted PIs (7.6%) — a pattern quite different from that seen in the U.S.

During 48 months of follow-up, median CD4 gains were 343 cells/mm³ among patients on boosted PI-based regimens, compared with 310 cells/mm³ among those on unboosted PIs and 255 cells/mm³ among those on NNRTIs. Based on the analytic approach used, these increases did not differ significantly from one another, even though the numerical differences appear to be meaningful. Among the subset of patients who achieved virologic suppression, median CD4 increases were 393 cells/mm³ in the boosted-PI group, 322 cells/mm³ in the unboosted-PI group, and 274 cells/mm³ in the NNRTI group; again, the differences were not significant after adjustment for other factors. Of note, patients in the boosted-PI group started with the lowest median pretreatment CD4 count (168 cells/mm³, compared with 201 cells/mm³ in the unboosted-PI group and 220 cells/mm³ in the NNRTI group). Factors independently associated with diminished CD4-cell responses included older age, prior NRTI treatment, hepatitis C virus coinfection, AIDS-defining conditions, lower baseline CD4-cell counts, and lower viral loads. The authors concluded that CD4-cell recovery was similar with all three treatment options.

Comment: Although researchers saw no significant differences in CD4-cell reconstitution among the various groups in this study, patients in the boosted-PI group consistently experienced the greatest numerical CD4-cell increases. This study was large and benefited from consistent follow-up, but the retrospective cohort design imposes some limitations. Most notable, patients treated with unboosted PIs made up more than three quarters of the treatment population, and the regimen was not randomly selected — the boosted-PI group had lower baseline CD4-cell counts and higher baseline viral loads than did the other two groups. The extensive use of unboosted PIs in this cohort limits the applicability of these results to many practice settings. The bottom line: Triple-drug combinations that include NRTIs plus either PIs (with or without ritonavir) or NNRTIs lead to meaningful and clinically significant improvements in CD4-cell recovery.

— **Charles B. Hicks, MD**

Khanna N et al. CD4⁺ T cell count recovery in HIV type 1-infected patients is independent of class of antiretroviral therapy. Clin Infect Dis 2008 Oct 15; 47:1093.

When First Regimens Fail, Resistance Patterns Vary

Genotypic drug resistance is widespread following failure of initial therapy with NNRTIs but not with boosted PIs.

In the ongoing search for the “best” initial antiretroviral combination, comparing the failure rates of different regimens is not enough. The reasons for failure are also important, because the resistance patterns that are created when initial antiretroviral treatment fails have powerful implications for the success of future treatments. In the present study (a meta-analysis), researchers assessed the differences between resistance patterns created by failed boosted PI-based combinations and those created by failed NNRTI-based combinations.

Twenty clinical trials were included in the analysis, yielding information on more than 7000 individuals who initiated antiretroviral therapy with either a boosted PI or an NNRTI, along with 3TC, FTC, and another NRTI. All the trials were conducted and reported between

2001 and 2007, and none involved ddI, ddC, nelfinavir, indinavir, or full-dose ritonavir.

Rates of virologic failure at week 48 were similar between patients who received NNRTIs and those who received boosted PIs (4.9% and 5.3%, respectively). However, according to genotype testing of 471 patients with virologic failure (180 on boosted PIs and 291 on NNRTIs), the NNRTI group had significantly higher rates of a wide range of resistance mutations. Not only was genotypic resistance to NNRTIs more common than resistance to PIs (53.0% vs. 0.9%), but the NNRTI group also had higher rates of important nucleoside resistance mutations: M184V was detected in 35.3% of the NNRTI group versus 21.0% of the boosted-PI group, and K65R was seen in 5.3% versus 0.0%. A trend toward more thymidine analogue mutations in the NNRTI group did not reach significance. Combining NNRTIs with newer NRTIs, such as tenofovir and abacavir, did not affect rates of resistance to NNRTIs or to 3TC.

Comment: This interesting study provides much food for thought. In the developing world, most initial regimens consist of NNRTI-based combinations, in part because they are less expensive. However, these findings raise the issue of the long-term costs of that tactic; an editorial suggests that wider availability of tools for detecting virologic failure early might help deflect at least some of these costs. For those of us who practice in the developed world, the study emphasizes the often forgotten point that virologic failure and resistance are two separate problems. In the case of patients with failure on PI-based regimens, we must remember that genotypic PI resistance is often not responsible; instead, we must assume that adherence failure is the culprit and address that aggressively.

— **Abigail Zuger, MD**

Gupta R et al. Emergence of drug resistance in HIV type 1-infected patients after receipt of first-line highly active antiretroviral therapy: A systematic review of clinical trials. Clin Infect Dis 2008 Sep 1; 47:712.

Campbell TB. Choice of an initial antiretroviral regimen in the resource-limited setting: The cost of virologic failure. Clin Infect Dis 2008 Sep 1; 47:723.

MEETING REPORT

Report from the 10th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV

An expert's take on the most clinically relevant findings presented at the conference

With each passing year of the HIV/AIDS epidemic, we learn more about the pathogenesis of HIV disease and of treatment-related complications. Some of the most important lessons from this year's International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV were on the pathogenesis of inflammation, fat loss, and bone metabolism in infected patients. All abstracts, as well as webcasts of the oral presentations, are available free of charge at <http://www.intmedpress.com/lipodystrophy>.

Inflammation and Cardiovascular Risk

Inflammation is suspected to contribute to increased risk for both AIDS- and non-AIDS-related outcomes in HIV-positive patients. To determine whether a link exists between inflammation and myocardial infarction (MI) specifically, Virginia Triant and colleagues reviewed registry data from a large U.S. health-care system [Abstract O-05]. They identified all individuals who had C-reactive protein (CRP) levels measured during a 10-year period; 487 were HIV-positive, and 69,870 were HIV-negative. Not surprisingly, elevated CRP levels were more common among the HIV-positive individuals. In a multivariate analysis, HIV infection and elevated CRP levels were each associated with a twofold increase in MI risk; the combination was associated with a fourfold increase in risk. Notably, CRP levels were not associated with HIV viral-load values or with smoking status in the smaller subset of patients with these data available. Overall, these findings suggest that CRP levels might help predict MI risk in HIV-positive patients.

Metabolic Complications of Antiretroviral Therapy (ART)

The role of specific antiretrovirals in the pathogenesis of metabolic changes remains an area of active investigation, especially now that we have agents in different classes that are comparable in their ability to suppress HIV replication. A number of studies have demonstrated that certain PIs lead to short-term

changes in glucose metabolism. In a well-designed, randomized, crossover study conducted by Paul Randell and colleagues, 16 HIV-negative men each received a 14-day course of lopinavir/ritonavir and a 14-day course of raltegravir [Abstract O-25]. The rate of glucose disposal dropped an average of 16% during lopinavir/r treatment (confirming earlier short-term studies) but did not change during raltegravir treatment. The long-term effect of these changes has not yet been determined in clinical studies. To date, significant changes in glucose metabolism have not been observed among HIV-infected patients treated with lopinavir/r, suggesting that compensatory mechanisms might overcome these short-term changes.

In another small study, Marta Boffito and colleagues examined the effect of two different dosages of ritonavir (100 mg once or twice daily) on adipophilin gene expression in HIV-negative volunteers [Abstract O-06]. Adipophilin inhibits cholesterol efflux from cells, and higher levels of this protein could lead to intracellular lipid accumulation and contribute to cardiovascular risk. Twice-daily dosing of ritonavir was associated with a 30% increase in adipophilin mRNA quantity in peripheral blood mononuclear cells, whereas once-daily dosing had no effect. These findings highlight the importance of distinguishing the differential effects of ritonavir doses, although the clinical significance of the effect seen in this study is not yet known.

ART and Lipodystrophy

Although treatment interruption is no longer recommended as a strategy for managing HIV infection, we continue to glean important insights from the treatment-interruption studies launched several years ago. In one such study, conducted by Esteban Martínez and colleagues, patients with lipodystrophy and CD4 counts >450 cells/mm³ on thymidine nucleoside-based ART were randomized to continue ART with a nonthymidine nucleoside or to stop ART until their CD4 counts fell below 350 cells/mm³ [Abstract O-11]. During

2 years of follow-up, greater increases in limb fat were seen among those randomized to stop ART. The magnitude of increase, although statistically significant, was small (<1 g). These findings raise the possibility that other agents in the regimens used could have contributed to lipodystrophy among those on continuous treatment. In any case, discontinuation of ART is not recommended as a strategy to manage lipodystrophy. The preferred approach is to use nonthymidine analogues in first-line therapy.

ART and Bone Metabolism

Bone metabolism is an area of investigation in which the relative contributions of specific antiretrovirals, underlying HIV infection, and traditional risk factors remain unclear. Results of a bone substudy reported by Andrew Carr on behalf of colleagues in the SMART trial highlight the role that ART may play in bone loss [Abstract O-19]. Patients in this trial were randomized to remain on continuous ART or to undergo treatment interruptions based on CD4-cell counts. Bone-mineral density (BMD) was assessed using dual-energy x-ray absorptiometry at baseline and then annually. Throughout 4 years of follow-up, the continuous-treatment group experienced a steady decline in BMD, whereas the intermittent-therapy group experienced an increase in the first year, followed by a steady decrease. At year 1 and year 2, the total percentage decline in BMD was greater in the continuous-treatment group than in the intermittent-therapy group. Additionally, rates of fractures (all reported fractures, without respect to trauma) were significantly greater in the continuous-treatment group than in the intermittent-therapy group (0.13 vs. 0.03 per 100 patient-years; hazard ratio, 4.9). These findings highlight the need for prospective studies comparing changes in bone density during ART; such studies are needed to help inform clinicians and patients about the contributions of different ART regimens to bone loss.

—Judith Currier, MD, MSc

Occult HBV Infection in HIV Patients

Occult HBV infection was rare in a cohort of HIV-infected patients and was not associated with elevated transaminase levels or with symptomatic liver disease.

Occult hepatitis B virus (HBV) infection is defined as the presence of HBV DNA in the absence of detectable hepatitis B surface antigen (HBsAg) in the blood. In some studies, occult HBV infection is associated with the presence of isolated antibody to hepatitis B core antigen (anti-HBc), which is a common finding in HIV-infected patients (*Clin Infect Dis* 2003; 36:1602). Now, investigators have examined the prevalence and clinical significance of occult HBV infection among HIV-infected patients with isolated anti-HBc.

In a cross-sectional study of 3030 HIV-infected patients in Spain, 202 (6.7%) had isolated anti-HBc. Of these individu-

als, only 5 (2.4%) had occult HBV infection. The mean HBV DNA level was 66 IU/mL (range, 15–112 IU/mL). Transaminase levels and rates of symptomatic hepatitis were similar between patients who did and did not have occult HBV infection. Of note, most patients were receiving at least one antiretroviral agent that also had activity against HBV: More than 85% were receiving 3TC or FTC, and 44% were receiving tenofovir.

Comment: Because most patients in this cross-sectional study were on antiretroviral agents that also have activity against HBV, the rate of occult HBV infection is likely to have been underestimated. In addition, the small number of individuals identified with occult HBV infection (5 total) makes it impossible to rule out the possibility that such infection is associated with liver disease. Finally, in many studies of occult HBV infection, including this one, investigators look for HBV DNA in the serum, but we know that HBV DNA can be detected in

the liver even when it is not found in the blood. The role of occult HBV infection in the development of liver disease remains uncertain (*J Hepatol* 2008; 49:652). To better clarify this role in HIV-infected patients, prospective studies that include evaluation before and after initiation of antiretroviral therapy are needed.

— **Rajesh T. Gandhi, MD**

Dr. Gandhi is Assistant Professor of Medicine at Harvard Medical School and Director of HIV Clinical Services and Education at Massachusetts General Hospital in Boston.

Palacios R et al. Very low prevalence and no clinical significance of occult hepatitis B in a cohort of HIV-infected patients with isolated anti-HBc seropositivity: The BHOI Study. HIV Clin Trials 2008 Sep/Oct; 9:337.

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