Expert Commentaries From IDSA 2010 and HIV 10*

Inside

New NNRTIs in development: TMC278 and lersivirine
- Data from ECHO and THRIVE generate interest in terms of gender and race P. 3

Vitamin D deficiency among HIV-infected patients
- Investigators relationship between vitamin D deficiency and disease progression P. 4

Data provide support for use of oral HIV test
- Data from studies of oral and finger-stick HIV tests found oral tests less sensitive but equally specific P. 8

Are HIV-infected persons aging faster?
- Study results find evidence of accelerated vascular aging P. 5

Reports from IDSA 2010 and HIV 10

IDSA 2010
October 21-24, 2010
Vancouver, British Columbia, Canada

The 48th Annual Meeting of the Infectious Diseases Society of America (IDSA 2010), held in Vancouver, British Columbia, Canada, on October 21-24, 2010, was a key educational gathering for infectious diseases and HIV professionals from around the world. While much of the HIV-related material was presented in the symposium and workshop format for which the meeting is known, there were several important oral abstract and poster presentations certain to be of interest to HIV providers.

HIV 10
November 7-11, 2010
Glasgow, United Kingdom

The 10th International Congress on Drug Therapy in HIV Infection (HIV 10, also known as the Glasgow meeting), held in Glasgow, United Kingdom, November 7-11, 2010, was the tenth biennial conference in Glasgow, United Kingdom. The conference is notable for its large, single-session format and provides an opportunity for HIV providers and researchers in the United Kingdom and continental Europe to hear updates on the latest clinical and scientific data on HIV, along with numerous keynote lectures from experts in the field of HIV medicine.

Current trends in HIV testing and linkage to care

Recognizing the risks associated with untreated HIV infection, clinicians have taken major steps to attempt to address the challenge of the large proportion of HIV-infected persons who have not been diagnosed, beginning with the 2006 revised HIV testing recommendations from the Centers for Disease Control and Prevention (CDC). Efforts to better understand the needs of the undiagnosed and those not adequately linked to medical care continue.

Two studies presented at IDSA 2010 addressed the current characteristics of the HIV-infected population in the United States, looking at the large proportion of patients who have been diagnosed with HIV infection and are either not in care or not receiving antiretroviral therapy (ART).

Reported increases in the population of patients with high CD4 cell counts not on ART. A presentation by researchers in Washington State pointed to the issues surrounding the increase in the numbers of HIV-infected persons who are diagnosed, have high CD4 cell counts, and are not on treatment.

Expert Commentaries From IDSA 2010 and HIV 10*

*This issue of POSITIVE PULSE is an independent CME/CE-certified activity commenting on findings from IDSA 2010 and HIV 10 and is not an official publication of the conferences.

Cover Story

Are HIV-infected persons aging faster?

Study results find evidence of accelerated vascular aging P. 5

Cover Story Illustration: The HIV proviral DNA entering the host T-cell's nucleus pore and preparing to infect the host T-cell's DNA structure within the nucleus.
Letter from the Editors

Dear Colleague,

As 2010 comes to a close, we wrap up the year with a review of some of the highlights of the recent 48th Annual Meeting of the Infectious Diseases Society of America (IDSA 2010) held in Vancouver, British Columbia, Canada and the 10th International Congress on Drug Therapy in HIV Infection (HIV 10) Conference held in Glasgow, United Kingdom. As always, the conference coverage is supplemented by commentary about the clinical significance of the data and how they might impact your clinical practice in the coming months.

In our lead story, we look at two recent cohort studies that present pictures of the current state of HIV testing and treatment. Data from the Center for AIDS Research (CFAR) Network of Integrated Clinical Systems (CNICS) illustrate the changing trends in HIV diagnosis, with increasing numbers of patients being diagnosed and started on antiretroviral therapy (ART). The national prescription data analyzed by Seekins et al suggest that a significant proportion of people are being diagnosed but not necessarily under the care of a clinician, and point to the challenge of linking patients to care after an HIV diagnosis.

A key focus at both IDSA 2010 and HIV 10 was the emerging data on the investigational nonnucleoside reverse transcriptase inhibitor (NNRTI) TMC278 (rilpivirine). With a high level of anticipation for this agent among both clinicians and patients, the data reported at both meetings provide encouraging information about the consistency of the virologic activity and pharmacokinetics of TMC278 across a wide variety of patient populations.

Heightened attention to the prevalence of vitamin D deficiency across patient populations continues to fuel research into its potential impact in patients with HIV. The data from the US military reported by Sherwood et al indicate a high prevalence of vitamin D deficiency among active-duty soldiers, particularly African Americans, but failed to find an association between low vitamin D levels and HIV infection. Nevertheless, in another study, researchers with the EuroSIDA cohort reported significant associations between low vitamin D levels and the risk of AIDS events and death among HIV-infected patients.

Another topic of increasing interest to clinicians is the accumulating evidence to suggest that the presence of HIV accelerates the aging process and consequently might contribute to the progress of some of the non-AIDS-defining conditions that are common among people with HIV. We report on a few recent studies that assess the impact of HIV on coronary artery disease and bone mineral density and how the effects of HIV infection compare with the natural aging process.

As clinicians, we are all seeking to provide the most effective treatment possible for our patients with HIV. Two studies explore the effects of provider and regimen characteristics and point to the important roles that both provider experience and the availability of compact dosing regimens have on adherence and clinical outcomes. In another article we review the latest information on the use of boosted protease-inhibitor monotherapy as an alternative to standard combination ART.

As we look toward 2011, we hope that this latest issue of POSITIVE PULSE will help to keep you up to date with the most recent developments in the field of HIV and support you in your efforts to provide your patients with the best possible HIV care.

Sincerely,

Sally Hodder, MD
Professor of Medicine
New Jersey Medical School
University of Medicine and Dentistry of New Jersey
Newark, NJ

Paul Sax, MD
Associate Professor of Medicine
Harvard Medical School
Clinical Director
Division of Infectious Diseases
and HIV Program
Brigham and Women’s Hospital
Boston, MA

Cover Story continued from page 1

Figure 1. Proportion of patients not on ART in CNICS, 2000-2008 (N = 31,659).


Editors’ Commentary

Dr Sax: It is encouraging to note that there is a growing body of literature showing that people are getting diagnosed at an earlier stage in their disease. For example, in this study the researchers found an increasing proportion of patients entering the cohort at CD4 cell counts of >500 cells/mm³. This is exactly what we were hoping for when the testing guidelines were changed. And this is something that has been seen not just in the United States, but also through much of the developed world. Earlier this year, a paper was presented at CROI 2010 about the improvements in testing in Washington, DC. These data also provide a counterweight to the widely cited data from Matthias Egger, which suggested that people start ART very late. It appears that this is not the case anymore, and that is the good news. On the other hand, recent CDC data showed that approximately one-third of people are getting diagnosed with HIV at a time when they have a complication of AIDS or advanced HIV-related immunodeficiency, so there is still work to be done here. The other issue is the fact that with more people entering care earlier, and treatment guidelines recommending treatment earlier, health care systems will be put under increasing strain to pay for the medications. A recent paper by Martin et al underlines this point. But the return on that is the possibility of avoiding AIDS progression and death, so obviously it is a cost well worth bearing.

Dr Hodder: I agree with Dr Sax. Several studies indicate that progress is being made in the domestic epidemic. CD4 cell counts are increasing as demonstrated by the CFAR cohort, and more people are initiating therapy. However, the CFAR cohort also demonstrates that a significant proportion of persons not on antiretroviral therapy have CD4 cell counts <350 cells/mm³. Major disparities in HIV outcomes in the United States persist. Fifty-six percent of HIV-infected persons in the United States who progress to AIDS within 1 year of diagnosis are African Americans. HIV-infected African Americans (both men and women) continue to have higher mortality rates, and analyses of multiple clinical trials have demonstrated that African Americans have significantly lower virologic response rates compared with their white counterparts. So, despite demonstrated progress, there is still much, much to do.

Survey suggests a large segment of the HIV-diagnosed patient population is not in care.

In another study presented at IDSA 2010, national prescription data were analyzed to arrive at an estimation of the total HIV-positive population receiving ART as of the end of 2008. The study’s objectives were to estimate the proportions of HIV-infected individuals in the United States who are in care and receiving ART, are ART-naïve, are between ART regimens, or who are not in care. The researchers gathered data from the Synovate US HIV Therapy Monitor Study, the CDC, and health care market-research firms.

Based on the data from Synovate, in the last quarter of 2008, 83% of patients were receiving ART, 3% were between regimens, and 14% were naive to treatment. The data from all sources were used to create a demographic map of the state of the US HIV epidemic in 2008 (Figure 2).

According to these data, the overall estimate of HIV-infected patients under the care of a physician in 2008 was 594,000, with 314,000 patients diagnosed and not in care. Based on these estimates, there were more people diagnosed but not in care than were undiagnosed according to CDC estimates. The investigators noted a need to further characterize this group of patients to better target resources to individuals who are not adequately linked to HIV care and treatment. They also commented that a similar study should be conducted to take into account the revision of the Department of Health and Human Services treatment guidelines, which increased the CD4 threshold for initiating ART to include patients with CD4 cell counts of 350-500 cells/mm³.
New NNRTIs in development: TMC278 and lersivirine

An analysis of the 48-week results of the ECHO (Efficacy comparison in treatment-naive HIV-infected subjects of TMC278 and efavirenz) and THRIVE (TMC278 against HIV in a once daily regimen versus efavirenz) studies presented at IDSA 2010 evaluated the influence of gender and race on the efficacy and tolerability of TMC278 (rilpivirine) and efavirenz (EFV) when both were combined with fixed-dose tenofovir dipivoxil fumarate (TDF)/emtricitabine (FTC) [ECHO] or investigator-selected TDF/FTC, zidovudine (AZT)/lamivudine (3TC), or abacavir (ABC)/3TC [THRIVE] in treatment-naive patients. ECHO and THRIVE are ongoing phase 3, double-blind randomized trials assessing the noninferiority of TMC278 compared with EFV in terms of confirmed virologic response at Week 48. In all, 1368 patients were enrolled in the two studies, with an overall median viral load of 5 log₁₀ copies/mL and a median CD4 cell count of 256 cells/mm³. Baseline characteristics were generally similar across study subgroups. At Week 48, the response rates were similar for men and women, with 84.6% and 83.3% of men and women, respectively, achieving virologic response on TMC278 and 81.9% and 83.4% of men and women, respectively, achieving virologic response on EFV. There were, however, statistically significant differences in virologic response rates among racial subgroups, with African American patients reporting the lowest rates of virologic response (Table 1). The investigators stated that the lower response rate among African American patients may have been because they had a higher rate of discontinuation due to other causes.

In terms of safety and tolerability, the findings were generally similar across gender and race subgroups, with similar incidence of adverse events (AEs) and grade 2 to 4 AEs.

Investigators reported the following exceptions:
- Headache occurred at a higher incidence in women versus men
- Diarrhea and abnormal dreams/nightmares were more common in men than women (in the EFV and both treatment arms, respectively)
- Dizziness was more common in Asian patients than in white or African American patients
- Abnormal dreams/nightmares were more common in white patients compared with other race groups
- Headache and diarrhea were more common among white and African American patients in the TMC278 arm

Overall, the study found no differences in virologic response according to gender in either treatment group. As has been reported in other HIV clinical studies, virologic response rates were lower among African American patients compared with other racial groups, which may have been due to higher rates of virologic failure and discontinuation due to other causes.

An additional analysis from the ECHO/THRIVE studies looked at the pharmacokinetic (PK) parameters of TMC278 and the impact of various intrinsic and extrinsic factors on the PK of the drug. To determine TMC278 plasma concentrations, venous blood samples were drawn every 4 weeks from Weeks 0 to 48 and every 24 weeks beginning at Week 24. A 24-hour TMC278 profile was obtained in a subset of patients at Week 4 or Week 8. The investigators then developed a population PK model for TMC278 based on data for HIV-infected patients and healthy volunteers receiving TMC278 25 mg once daily, and applied the model to the data. Further information regarding not only the etiology of existing health disparities in HIV outcomes but also effective interventions to eliminate these disparities. The higher virologic failure rate in the TMC278 arms of ECHO and THRIVE has led to speculation that these failure rates may have been lower if a higher TMC278 dose had been used. Though early dose-ranging data clearly support selection of a TMC278 dose of 25 mg daily, the dose selection was actually dictated by the presence of QT prolongation other causes.

Figure 2. Demographic map: state of the US HIV epidemic, 2008.

**Table 1. ECHO and THRIVE pooled response rates at Week 48 according to gender and race (ITT-TLOVR)**

<table>
<thead>
<tr>
<th>Gender and Race</th>
<th>TMC278 (%)</th>
<th>Efavirenz (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>84.6</td>
<td>81.9</td>
</tr>
<tr>
<td>Women</td>
<td>83.3</td>
<td>83.4</td>
</tr>
<tr>
<td>White</td>
<td>85.5*</td>
<td>82.0*</td>
</tr>
<tr>
<td>Black or African American</td>
<td>75.2</td>
<td>74.4*</td>
</tr>
<tr>
<td>Asian</td>
<td>94.9*</td>
<td>92.8*</td>
</tr>
</tbody>
</table>

*P < 0.002 for comparisons across race. ITT-TLOVR, intent-to-treat time to loss of virologic response.

**Editors’ Commentary**

**Dr Sax:** It is encouraging to note that it has become standard practice to have analyses of clinical trials looking at response rates based on gender and race. In this study, you see effectively no differences in the treatment responses between the two drugs based on gender and race. Furthermore, if you do see a lower response rate in the African American patients, I suspect it has to do with sociodemographic factors rather than biologic differences, although that remains to be seen. Importantly, there were no differences between men and women, which echoes the results of the large Food and Drug Administration meta-analysis that looked at registrational studies of more than 20,000 patients and found no difference in the response rates between men and women that has been my impression clinically and anecdotally, so it is good to see it supported in clinical trials.

**Dr Hodder:** Multiple analyses of prospective randomized trials of antiretroviral drugs in both antiretroviral-naive and -experienced patients have demonstrated significantly lower rates of virologic success in African American/black persons compared with their white counterparts. The National Minority AIDS Council issued a very thoughtful report in which the following factors were identified as being associated with poor outcomes in HIV-infected African Americans: diagnosis at advanced disease stage, presence of comorbidities including mental illness and substance abuse, environmental factors such as homelessness, and distrust of the medical establishment. Moreover, in a study of black men who have sex with men (in the EFV with men, roughly one-third held conspiracy beliefs (eg, HIV was created by the government) regarding HIV and these beliefs were associated with significantly lower rates of adherence in a multivariate analysis. Clearly, further research is needed regarding not only the etiology of existing health disparities in HIV outcomes but also effective interventions to eliminate these disparities. The higher virologic failure rate in the TMC278 arms of ECHO and THRIVE has led to speculation that these failure rates may have been lower if a higher TMC278 dose had been used. Though early dose-ranging data clearly support selection of a TMC278 dose of 25 mg daily, the dose selection was actually dictated by the presence of QT prolongation other causes.

**Table 1. ECHO and THRIVE pooled response rates at Week 48 according to gender and race (ITT-TLOVR)**

<table>
<thead>
<tr>
<th>Gender and Race</th>
<th>TMC278 (%)</th>
<th>Efavirenz (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>84.6</td>
<td>81.9</td>
</tr>
<tr>
<td>Women</td>
<td>83.3</td>
<td>83.4</td>
</tr>
<tr>
<td>White</td>
<td>85.5*</td>
<td>82.0*</td>
</tr>
<tr>
<td>Black or African American</td>
<td>75.2</td>
<td>74.4*</td>
</tr>
<tr>
<td>Asian</td>
<td>94.9*</td>
<td>92.8*</td>
</tr>
</tbody>
</table>

*P < 0.002 for comparisons across race. ITT-TLOVR, intent-to-treat time to loss of virologic response.

Continuing research into the significance of vitamin D deficiency among HIV-infected patients

Lower serum vitamin D levels common among African American HIV patients and age-matched controls. A study by researchers from the Walter Reed Army Medical Center presented at IDSA 2010 did not find an association between HIV infection and vitamin D deficiency among men receiving military health benefits, a finding that differs from a study conducted by researchers from the University of Pittsburgh. However, a study presented at the 3rd European AIDS Conference (EACS) in 2009 did not find an association between vitamin D deficiency and HIV infection.

The investigators concluded that the association in African American men receiving military health benefits may be due to the fact that African American men are more likely to be vitamin D deficient due to a combination of factors, including limited sun exposure and limited access to food sources rich in vitamin D. In contrast, African American men receiving military health benefits are more likely to be vitamin D deficient due to the fact that they have a higher prevalence of obesity and diabetes, both of which are associated with reduced vitamin D levels.

New NNRTIs in development continued from page 3

New data on lersivirine, a novel NNRTI.

An in vitro study of the new nonnucleoside reverse transcriptase inhibitor (NNRTI) lersivirine presented at HIV 10 indicated potential activity against virus with resistance to etravirine (ETR), tenofovir disoproxil fumarate (TDF), and abacavir (ABC). In addition, the study included 19 viruses with NNRTI resistance mutations as well as 43 non-resistant viruses from patients. The study also included 19 viruses with NNRTI resistance mutations as well as 43 non-resistant viruses from patients. The study found that lersivirine was found to be active against 80 clinically selected patients in the EuroSIDA cohort.

The researchers also found that 18/228 patients with vitamin D levels below 20 ng/mL were more likely to have a higher risk of AIDS-related death. The study was a follow-up to a previous study that found a higher risk of AIDS-related death in patients with vitamin D levels below 20 ng/mL.

Editors’ Commentary

Dr Sax: HIV drug development now includes assessing the potential impact of investigational drugs on QTc interval using a single 2400 mg supertherapeutic dose of lersivirine. Although phase 1 studies have not found any effect on QTC interval or any other electrocardiographic (ECG) parameters, in vitro studies suggest that lersivirine is a weak potassium channel blocker. In this randomized, placebo-controlled, three-way crossover study, 48 healthy adults were randomized to receive a single dose of either lersivirine (2400 mg), mosfloxacin (400 mg), or placebo followed by a minimum washout period of 7 days. ECG measurements were performed in triplicate, and investigators collected PK samples predose, hourly for the first 6 hours, and at 9, 12, and 24 hours post-dose. Subjects were monitored for clinical and laboratory adverse events (AEs) throughout the study period. All subjects were white males, with a mean age of 39.1 years and a mean body mass index of 25.6 kg/m². Following administration of lersivirine, there was no statistically significant relationship between lersivirine exposure and placebo-adjusted change from baseline corrected QTc (QTcF) interval. Overall, no significant differences in any ECG parameters (QTcF, QTcE, uncorrected QT, PR, QRS), blood pressure, or heart rate were reported in the subjects receiving lersivirine. None of the subjects receiving lersivirine had an absolute maximum QTcF interval of 450 ms or greater than 50 ms change from baseline QTcF. In all, 71 mild-to-moderate AEs were reported (46 in the lersivirine arm and 25 in the placebo group). The investigators concluded that since lersivirine has no clinically relevant effect on the QTcF interval or any other ECG parameters, it can be safely administered without requiring ECG monitoring.

Figure 3. Univariate and multivariate incidence rate ratios of AIDS, death, and non-AIDS events by vitamin D levels, EuroSIDA cohort.


**Adjusted for baseline values of gender, ethnic origin, HIV risk group, region of Europe, HBsAg and HCV antibody status, prior AIDS diagnosis to antiretrovirals, age, CD4 count, CD4% at entry, HIV-RNA viral load, date of baseline sample date, season of sample, and date of recruitment to EuroSIDA.

Editors’ Commentary

Dr Sax: Regardless of what disease state or what population you look at, you find a fairly high rate of vitamin D deficiency. This military cohort study found that rates of vitamin D deficiency are higher among people of African descent. However, the researchers did not find a difference in the rate of vitamin D deficiency in HIV-positive versus HIV-negative patients, and also found no correlation between vitamin D levels and low CD4 count. Many questions remain. I would suggest that, for now, measurement of vitamin D is a reasonable strategy, especially in African American patients, but should it be a standard part of primary care?

Dr Hodder: There have been a plethora of papers in the noninfectious disease literature associating low vitamin D levels with multiple maladies including certain cancers, cardiovascular disease, and all-cause mortality. So, in many ways, the association of low vitamin D levels with mortality in HIV-infected persons in the ID-rosIDA study is hardly surprising. What is unknown is whether supplementing vitamin D in persons with low levels will improve mortality and outcomes other than fractures (eg, decrease the incidence of the associated cancers and cardiovascular disease). I do not think we yet know the best strategy for dealing with vitamin D deficiency in the persons, of adult HIV medicine. Multiple approaches have been suggested, including screening everyone for low vitamin D levels or supplementing everyone with 1000-2000 IU/day of D without screening. Hopefully, ongoing studies will provide guidance in the near future for this difficult issue.
Long-term safety of once-daily ART

In the current environment, patients with HIV who begin antiretroviral therapy (ART) are generally facing many years and perhaps decades of drug treatment to control the virus. The success of such treatment over the long term is largely dependent on maintaining adequate adherence. At HIV 10, researchers presented the 5-year safety and efficacy data from Study 934, comparing once-daily efavirenz (EFV)/emtricitabine (FTC)/tenofovir (TDF) with EFV plus twice-daily zidovudine/lamivudine (AZT/3TC) in treatment-naïve patients. The current analysis looks at the efficacy and safety data for 160 subjects who were randomized to receive EFV/FTC/TDF, completed 144 weeks of the original trial and agreed to continue on the single-tablet formulation of EFV/FTC/TDF and remain in the study for another 96 weeks. At baseline, the mean HIV RNA was 5.03 log₁₀ copies/mL and the mean CD4 cell count was 243 cells/µmm³; 88% of the patients had symptomatic HIV or AIDS. At the end of 240 weeks, 84% had HIV RNA < 50 copies/mL and the mean increase in CD4 cells from baseline was 346 cells/µmm³. This study included an ad hoc adherence analysis, which reported a mean adherence rate of 97.9% with the single-tablet regimen. Over the course of the study 17 subjects discontinued EFV/FTC/TDF, though no discontinuations were due to renal adverse events. The mean change from baseline in estimated GFR (Cockcroft-Gault) was -7 mL/min.

The investigators concluded that the data point to earlier onset of coronary artery disease among HIV-infected persons compared to the non-HIV-infected population, and suggested that HIV-infected patients may benefit from early cardiovascular evaluation.

Editors’ Commentary

Dr Sax: The important take-home message here is that there does seem to be evidence of accelerated vascular aging in patients with HIV compared to HIV- negative controls. This is probably multifactorial and may be due to chronic inflammation and immune activation, as well as risk factor issues such as the high prevalence of cigarette smoking and dyslipidemia in HIV-positive patients. I think that the finding of fatty liver disease is interesting since that is another condition that correlates with immune activation and inflammation.

Dr Hodder: The cross-sectional design of this study does not allow for an understanding of the relationship between inflammatory biomarkers and vascular aging; however, the observation of accelerated vascular aging in HIV-infected patients is sure to stimulate future studies designed to better assess the contribution of these various parameters. It is clear that the current field of inquiry regarding accelerated aging in HIV-infected persons will substantively contribute to the overall understanding of age-related morbidity in the general population.

Antiretroviral therapy exposure and mitochondrial aging. It is thought that the normal aging process in humans is driven by the progressive accumulation of molecular defects, including those in mitochondrial DNA (mtDNA). Given the known impact of some nuclease reverse transcriptase inhibitors (NRTIs) on mitochondria, researchers in the United Kingdom studied HIV-infected patients with exposure to antiretroviral agents to assess whether treatment with NRTIs might affect age-associated mtDNA mutation. HIV-infected patients older than 50 years with substantially reduced bone mineral density (BMD) is well documented in people with HIV. A cross-sectional study in the United Kingdom was designed to compare changes in BMD among HIV-infected patients and healthy controls. The study presented at HIV 10, included 223 randomly selected HIV-infected patients stratified by gender and age group (50-39 years, 40-49 years, and 50 years and older) and age-matched controls. Patients completed a detailed questionnaire about their antiretroviral therapy (ART) history and were given a dual-energy X-ray absorptiometry (DEXA) scan of the lumbar spine and the left hip, along with a panel of laboratory assessments. The study also recorded risk factors for decreased BMD plus the success of such treatment over the long term is largely dependent on maintaining adequate adherence. At HIV 10, researchers presented the 5-year safety and efficacy data from Study 934, comparing once-daily efavirenz (EFV)/emtricitabine (FTC)/tenofovir (TDF) with EFV plus twice-daily zidovudine/lamivudine (AZT/3TC) in treatment-naïve patients. The current analysis looks at the efficacy and safety data for 160 subjects who were randomized to receive EFV/FTC/TDF, completed 144 weeks of the original trial and agreed to continue on the single-tablet formulation of EFV/FTC/TDF and remain in the study for another 96 weeks. At baseline, the mean HIV RNA was 5.03 log₁₀ copies/mL and the mean CD4 cell count was 243 cells/µmm³; 88% of the patients had symptomatic HIV or AIDS. At the end of 240 weeks, 84% had HIV RNA < 50 copies/mL and the mean increase in CD4 cells from baseline was 346 cells/µmm³. This study included an ad hoc adherence analysis, which reported a mean adherence rate of 97.9% with the single-tablet regimen. Over the course of the study 17 subjects discontinued EFV/FTC/TDF, though no discontinuations were due to renal adverse events. The mean change from baseline in estimated GFR (Cockcroft-Gault) was -7 mL/min.

Long-term safety continues on page 6

Are HIV-infected persons aging faster?

With studies showing increased rates of major heart-defining diseases (including cardiovascular disease, osteoporosis, and cognitive dysfunction) among the HIV-infected, clinicians and researchers have asked if this might be the result of an accelerated aging process associated with HIV (eg, via HIV-induced inflammation), antiretroviral modifications, or comorbidities. With cardiovascular disease, in particular, getting a better understanding of the risk of accelerated coronary artery aging in HIV-infected patients may help develop screening and preventive guidelines. The results of a cross-sectional study among HIV-infected adults presented at IDSA 2010 found evidence of accelerated vascular aging that may contribute to the increased morbidity from cardiovascular disease in the HIV-infected population. It is studied looked at 223 HIV-infected adults with a median age of 43 years; 96% were male, and 49% were white. They had a median CD4 cell count of 558 copies/mL and had been infected with HIV for a median of 12 years. Study participants underwent computed tomography for coronary artery calcium scoring (CAC—a marker for future cardiovascular events) and to assess for fatty liver disease. The study found that 75/223 patients (34%) had a positive CAC score (>0). Increased coronary age was observed in 67% of patients (30%) with a median increase in vascular age of 18 years above chronological age. Looking at the results by age, 3% of patients aged 20 to 30 years, 2% of those aged 30 to 39 years, 3% of those aged 40 to 49 years, and 46% of those older than 50 years had elevated coronary age. In multivariate analysis both fatty liver disease and increased chronological age were significantly associated with increased coronary age (Table 2).

Table 2. Multivariate model of factors associated with increased coronary aging among HIV-infected persons

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronologic age (per 10 years)</td>
<td>2.6</td>
<td>(1.8, 3.9)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Fatty liver disease</td>
<td>4.4</td>
<td>(1.9, 10.5)</td>
<td>.001</td>
</tr>
<tr>
<td>C-reactive protein (&gt; 0.5 mg/dL)</td>
<td>2.3</td>
<td>(1.0, 5.4)</td>
<td>.05</td>
</tr>
</tbody>
</table>

P value: < .001. OR: odds ratio.

The study, presented at HIV 10, found that CD levels increased with age among all patients (r = 0.467, P = .005). Among those with a history of exposure to NRTIs, mean CD levels were significantly higher than those observed in the unexposed patients (mean log₁₀(CD/mtDNA) ± SEM: NRTI-positive, -3.46 ± 0.24; NRTI-negative, -4.62 ± 0.29; P = .006). In addition, lifetime NRTI exposure was predictive of CD level (r = 0.419, P = .002). The investigators demonstrated via in silico modeling that a limited period of partial replication failure led to a period of mtDNA depletion that appeared to correspond to the expected exposure that correlated with the relevant NRTI. Further, they observed rapid expansion of pre-existing mtDNA deletions during the period, which led to an increase in the proportion of cells with a mitochondrial defect that continued after the NRTI exposure. The study also evaluated the impact of exposure to certain NRTIs appears to accelerate the accumulation of mtDNA deletion mutations typically associated with aging. The process is irreversible and is similar to what is expected much later in life due to the normal aging process. The most profound effects of NRTI exposure were observed with longer exposure, exposure to more potent inhibitors of mtDNA replication, and exposure later in life.

Editors’ Commentary

Dr Sax: Several studies have been conducted with similar design, all of them finding surprisingly high rates of low bone density in patients with HIV. In addition, the association with ART has also been consistent, and this was notably one of the few benefits associated with treatment interruption in the SMART study. While the most recent revision of the HIV primary care guidelines did not recommend DEXA scans as a matter of routine, it is important to consider triggering such testing in any situation where BMD is abnormal. However, cART was significantly associated with abnormal BMD (adjusted odds ratio [OR], 4.43; 95% confidence interval [CI], 1.57, 12.50; P = .005). Both the HIV-infected patients and controls had mean 10-year FRAX scores < 5% (3.16 and 2.0% in the HIV-infected and controls, respectively). The mean RLFP for the spine was significantly higher among antiretroviral-treated HIV-infected persons versus controls (Table 3).

The unadjusted OR for RLFP of the spine among HIV-infected patients was 1.22 (95% CI, 1.09, 1.40; P = .01). Looking at those not on ART as compared with those on treatment, the RLFP for spine and femoral neck was significantly higher among those receiving cART (OR 1.41, 95% CI, 1.07, 1.86; P = .01). Among those on cART compared with those not on treatment, the RLFP for spine and femoral neck was significantly higher among those receiving cART (OR 3.45, 95% CI, 1.98, 5.91; P < .01). Among those on cART compared with those not on treatment, the RLFP for spine and femoral neck was significantly higher among those receiving cART (OR 3.45, 95% CI, 1.98, 5.91; P < .01). Overall, the investigators reported a high proportion of HIV-infected patients younger than 50 years with substantially reduced BMD. They also found an increased RLFP for the spine associated with HIV infection. Among HIV-infected patients, cART treatment was associated with a higher predicted lifetime risk of a fracture. An additional important consideration is the need to better define factors that are most strongly associated with an increased risk of fractures in people living with HIV.
**Boosted PI monotherapy: a viable strategy?**

Meta-analysis of PI monotherapy studies finds small but significant advantage for combination antiretroviral therapy (cART). Clinicians and researchers continue to study the potential efficacy and safety of ritonavir-boosted protease-inhibitor (PI) monotherapy. A recent meta-analysis of studies comparing monotherapy and standard PI-based cART, presented at HIV 10, found that PI monotherapy was 6% less effective than cART. Based on a review of published and unpublished studies from January 1993 to 2010 and on a search of conference ab- stracts from 2007, investigators compiled the relevant data from 6 publications and 4 conference abstracts, representing a total of 10 randomized controlled trials. Using statistically anal- ical analysis, the investigators found that PI monotherapy resulted in 6% less virologic suppression: the summary Mantel Haenszel report effect relation risk estimate (RR) for the outcome of viral suppression (<50 copies/mL) on boosted PI monotherapy versus cART by intent-to-treat analysis was 0.94 (95% confidence interval [CI], 0.89-0.99). According to an on-treatment analysis, which censored missing data, deaths, and drug changes due to adverse events, the RR was 0.95 (CI, 0.85, 0.96), with 913 participants.

The report acknowledges all studies were open label and there was variability in both study populations and treatments in- terventions. The investigators suggest that while boosted PI monotherapy is slightly but significantly less effective than cART, it may be beneficial in certain subgroups of patients. A further analysis of the results of the MONET trial, which enrolled 256 patients on current stable cART and switched them to either once-daily darunavir/ritonavir (DRV/r) monotherapy or DRV/r + 2 nucleo- side reverse transcriptase inhibitors (NRTIs), reported similar levels of HIV RNA suppres- sion with the two regimens. Using the Roche Amplicor Ultrasensitive assay combined with Coprider, Deng and colleagues demon- strated durable virologic suppression over the course of the 240 weeks, as did cART monotherapy. Plasma samples were drawn and stored to the time of second-line therapy, after 24 weeks of second-line treatment, and then 24 weeks after random- ization to either continued cART or boosted PI monotherapy. Samples were then tested for HIV RNA and genotypic resistance (sam- ples with viral load >1000 copies/mL).

In all, 192 patients were randomized to continued cART (n = 95) or boosted PI monotherapy (n = 97). At 24 weeks after ran- domization, a higher proportion of patients receiving cART had HIV RNA <50 copies/ mL (77% [70/91] vs 60% [56/94], respectively). Patients in the cART and boosted PI monotherapy groups, respectively; P = .007). Looking only at those patients who had HIV RNA <50 copies/mL at randomization, 85% (57/67) versus 66% (43/65) of the cART and boosted PI mono- therapy groups, respectively, had viral loads <50 copies/mL at Week 24. In terms of re- sistance, of the 12 patients with HIV RNA >1000 copies/mL at Week 24 for whom there were genotypic tests available, 2 were in the cART arm and 10 were in the boosted PI monotherapy arm; major mutations were found in 2 of the boosted PI monotherapy patients only. However, both isolates were considered to be fully susceptible to darunavir. The investigators concluded that boosted PI monotherapy following 24 weeks of cART may be an option in patients no longer tolerating PI-based regimens.

Long-term safety of once-daily ART continued from page 5

In addition, fasting lipids remained stable over the course of the 240 weeks, as did median total limb fat. Overall, the regimen demonstrated durable virologic suppression and significant increases in immunologic function over the 5 years of the study, with a relatively low rate of discontinuation, and stable safety parameters. Adding to the safety and efficacy picture of once-daily nonnucleoside re- verse transcriptase inhibitor (NNRTI)-based ART are the 10-year safety and efficacy data from the open-label extension of Study 903. Study 903 was a 3-year phase 3 study com- paring TDF to stavudine (d4T), each com- bined with 3TC and EFV. As in Study 934, patients who completed the original 3-year study were eligible to roll over into an open- label study of TDF + 3TC + EFV. At the open- label baseline, 86 patients who were origi- nally randomized to TDF continued into the open-label phase. As a group, they were 62% male, 70% white, with a mean age of 33 years. They had a mean HIV RNA of 4.9 log10 c/mL, and a mean CD4 cell count of 299 cells/mm3. In addition, 85 patients originally randomized to d4T chose to roll over into the open-label extension and receive TDF + 3TC + EFV for the remainder of the study (d4T/TDF group). The results pre- sented for the d4T/TDF group show changes from the open-label baseline (Week 144) to week 480. That group of patients was 60% male, 64% white, with a mean age of 37 years. They had a median CD4 cell count of 621 cells/mm3. Both groups saw signifi- cant increases in mean CD4 cell counts from baseline and substantial improvements in limb fat over the course of the study. Patients in the TDF/TDF group had small but statis- tically significant changes in mean spine and hip bone mineral density (BMD) from baseline (-2.44% and -2.94%, respectively), that occurred during the first year of therapy and then remained stable. Those in the d4T/ TDF group had a significant change only in mean hip BMD (-1.86%). Overall, the re- sults of this study demonstrate the long-term safety and efficacy of once daily ART with EVF + TDF + 3TC.

---

**Editors’ Commentary**

**Dr Sax:** Neither one of these long extension studies provides surprising data, yet they are important nonetheless. As patients are likely to be on ART for decades, the more information we have from long-term clinical trials about the safety and efficacy of our commonly used regimens, the more informed we can be about selecting the most ap- propriate treatments. Because these were phase 3 studies of tenofovir, the renal and bone data are particularly important. Regarding the latter, as has been shown previously, bone density does decrease initially, but then appears to stabilize over time.

**Dr Hodder:** Given the durability of current antiretroviral regimens, patients may take a given regimen for many years. Clearly, long-term safety data such as these are very reas- suring to patients as well as providers.

---

**Table 4. Percentage of HIV RNA 50 copies/mL and below at Week 96**

<table>
<thead>
<tr>
<th>HIV RNA</th>
<th>DRV/r Monotherapy</th>
<th>DRV/r + 2 NRTIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV RNA &lt;50 copies/mL, OD = background</td>
<td>79.0%</td>
<td>80.7%</td>
</tr>
<tr>
<td>HIV RNA &lt;50 copies/mL, detectable</td>
<td>17.1%</td>
<td>14.9%</td>
</tr>
<tr>
<td>HIV RNA 50-400 copies/mL</td>
<td>2.9%</td>
<td>3.5%</td>
</tr>
<tr>
<td>HIV RNA &gt;400 copies/mL</td>
<td>1.0%</td>
<td>0.9%</td>
</tr>
</tbody>
</table>


---

**Editors’ Commentary**

**Dr Sax:** Boosted PI monotherapy as a simplification strategy for patients who have achieved virologic suppression has been a topic of recent interest. It is practical in some subgroups of patients. The results of the meta-analysis and the DART study confirm earlier work that shows a small virolog- ic advantage to combination therapy over monotherapy. In essence, what has yet to be proven is that reducing therapy to boosted PI treatment alone confers a significant benefit to the individual beyond the cost savings of not being on three active drugs. In addition, there have been case reports of apparent “CNS escape” viral replication when this strategy is employed. While I am aware there is a great deal more enthusiasm for boosted PI monotherapy in Europe than in the United States, thus far I do not believe the clinical studies have provided a compelling reason to choose this strategy; except for a very limited number of patients who cannot tolerate NRTIs or other active drugs.

**Dr Hodder:** There appears to be a difference in patient outcomes in the MONET study compared with the DART study, likely attributable to patient selection. Patients in the MONET study had neither previous virologic failure nor previous darunavir exposure, and were required to have suppressed HIV RNA <50 copies/mL for at least 6 months before randomization to either boosted darunavir monotherapy or ritonavir-boosted cART. In contrast, DART participants were on second-line therapy with ritonavir-boosted lopin- navir-containing regimens and were randomized to boosted PI monotherapy 24 weeks after switching to this second-line regimen without the benefit of HIV RNA viral load determinations. Subsequent analysis in DART demonstrated that only 77% of the study population had undetectable HIV RNA viral loads at the time of monotherapy randomization. In DART, when considering outcomes of only those individuals with HIV RNA <50 copies/mL at switch, the cART arm had greater virologic suppression rates at 24 weeks compared with the boosted PI monotherapy arm (85% vs 66%, respectively). MONET 96-week efficacy data (presented atIAS 2010 in Vienna) demonstrated 74.8% of mono- therapy patients versus 80.6% of cART patients had HIV RNA <50 copies/mL when change of ART was considered failure. However, when the analyses included patients in whom ART was switched (ie, NRTIs were re-added to patients on monotherapy who had detectable HIV RNA viral loads), then 90.7% of the patients in the combination arm compared with 82.1% in the monotherapy arm had suppressed HIV RNA <50 copies/mL. I have to admit that I have not been an advocate of PI monotherapy; however, over time I have become convinced that it may be a feasible strategy in a small subset of patients who have very special financial or toxicity constraints. There is no doubt that cART is more effective than PI monotherapy. Nevertheless, carefully selected and monitored patients may do quite well with this strategy.
Impact of provider and regimen characteristics on adherence and HIV-related outcomes

In the early combination antiretroviral therapy (cART) era, studies suggested that infectious disease (ID) specialists and providers with greater numbers of patients and more experience treating HIV were more likely to prescribe cART and more likely to stress the importance of ART adherence with their patients. A recent retrospective cohort analysis from researchers at Kaiser Permanente California looked at how those relationships between provider characteristics and HIV treatment practices are evolving in the modern cART era. The study, presented at IDSA 2010, analyzed characteristics for 533 providers and 7597 HIV-infected patients initiating cART between 1997 and 2006. The provider characteristics were taken from provider surveys and HIV registry records, and included years of HIV treatment experience, specialty, and the size of the providers’ HIV patient populations. Patients were followed for 24 months following initiation of cART with adherence measured during the first 12 months of cART by pharmacy dispenses. The last HIV RNA measure at 12 and 24 months was used to assess HIV RNA below the limit of quantification (BLQ).

While having a larger HIV patient population was associated with better adherence in the unadjusted analysis, it had no impact in the adjusted analysis, in which more recent initiation of cART and use of the nonnucleoside reverse transcriptase inhibitor (NNRTI)-based NNRTI class were most strongly associated with greater adherence. However, having more HIV patients was significantly associated with a greater chance of having undetectable HIV RNA 12 months following cART initiation among those providers with more than 10 HIV patients. At both 12 and 24 months post-cART initiation, a greater likelihood of having HIV RNA below the limits of detection was most strongly associated with NNRTI class and more recent initiation of cART (the latter at 24 months only). Somewhat surprisingly, neither provider specialty nor years of treating HIV had a positive association with either adherence to cART or the likelihood of maximal viral control. The investigators acknowledged that the data were limited by their retrospective nature and the lack of any documentation regarding provider-patient communication about adherence or the decision-making process around choice of cART.

The results of another study presented at HIV 10, based on recent data from an insurance claims database in the United States, found that treatment with an ART regimen consisting of 1 pill per day was associated with better adherence and a lower risk of hospitalization. The study included data from 7073 patients with a diagnosis of HIV between 2006 and 2008 who were receiving an ART regimen that included 2 NNRTIs and a third agent (NNRTI, protease inhibitor [PI], CCR5 antagonist, or integrase inhibitor). Patients were grouped according to daily pill count (1 pill per day, 2 pills per day, or 3 or more pills per day) and had to be on their regimens for at least 90 days. The study looked at adherence outcomes and rates of hospitalization according to number of pills per day in the regimen and attempted to control for potential confounding factors that might be associated with poor adherence (e.g., treatment experience, a history of psychiatric disease, substance abuse, female gender). A significantly higher percentage of patients in the 1 pill per day group (47%) achieved 95% adherence compared with patients in either the 2 pills per day (41%) or 3 or more pills per day groups (34%) (P < .05) (Figure 4). Using an estimated logistic regression analysis, patients were grouped according to pill count (1 pill per day, 2 pills per day, or 3 or more pills per day). The patients achieving at least 95% adherence had a lower rate of hospitalization compared with those in the 3 or more pills per day group (odds ratio [OR] = 1.62, P < .001).

Patients who achieved at least 95% adherence had a lower rate of hospitalization compared with those with less complete adherence. Based on estimated logistic regression analysis, those in the 1 pill per day group were 24% less likely to be hospitalized compared with patients in the 3 or more pills per day group (OR = 0.76, P < .01).

Editors’ Commentary

Dr Sax: I find this area very interesting, especially as it relates to the provider characteristics. This group found that certain factors were associated with better treatment outcome. I think we should focus on the outcome that we really care about— virologic suppression. In this study, having more HIV-positive patients was significantly associated with a greater chance of having undetectable HIV RNA. So there is the physician factor as well as the factor of being on an NNRTI regimen. The message for me is that even now when treatment is so successful, even now that treatment is so simple, it still makes sense to be an experienced HIV provider, whether they are called an ID specialist or HIV specialist or a primary care doctor with an interest in HIV. HIV still should be managed by clinicians who have a significant volume of patients.

Dr Hodder: The association of NNRTI with virologic suppression is not surprising. At 48 weeks, prospective randomized trials have never demonstrated superiority of a non-efavirenz (non-EFV) regimen compared with an EFV-containing regimen. However, superiority of EFV-containing regimens compared with lopinavir/ritonavir-containing regimens was demonstrated in ACTG 5142. I have always attributed the excellent efficacy of EFV regimens to its “forgiveness” of missed doses as suggested by the pharmacokinetics of efavirenz and shown by the P150 [Five On, Two Off)] study. However, the data presented by Horberg et al show better adherence (as measured by prescription refill data), perhaps attributable to one-daily dose and pill burdens.

The issue of provider experience and patient outcomes is an interesting one. I am not convinced that management of the uncomplicated HIV patient on first-line therapy requires an infectious disease specialist. As ART has gotten simpler and patients are suppressed on first-line regimens for many years, uncomplicated patients are likely to be managed effectively by diligent primary care providers.

Editors’ Commentary

Dr Sax: In this study, my colleagues and I looked at a large payer-based database to assess the correlation between a 1 pill per day regimen, a 2 pills per day regimen, or a 3 or more pills per day regimen, and adherence. It is important to note that there are all kinds of potential confounders here, since people who are treatment-experienced are more likely to require more complex regimens. In addition, it is well known that providers sometimes preferentially give boosted PI-containing regimens to patients they think are going to be nonadherent. However, we tried to control for these confounders by looking at other conditions that might go along with poor adherence, such as diagnoses of mental illness or substance abuse. Even when you control for those factors, having a 1 pill per day regimen was statistically associated with better adherence and a lower risk of hospitalization. A similarly strong finding for single pill per day regimens was observed in the study of marginally housed patients in San Francisco by Bangsberg et al. Not surprisingly, several potential single pill regimens are currently under investigation in phase 3 studies, most notably the combination of TDF/FTC/rilpivirine and TDF/FTC/elvitegravir/cobicistat.

Dr Hodder: Kudos to my colleague Dr Sax for performing this important study. As many of the components of antiretroviral regimens are already off patent or will be so over the next several years, it is possible that third-party payers will not support the more expensive options of fixed-dosed combinations despite the fact that they are more convenient for patients. It is critical that studies assess whether the fixed-dose options translate to improved outcomes. Not only did this study demonstrate improved adherence, it also demonstrated that persons taking a once-daily fixed-dose combination pill had a lower risk of hospitalization compared with persons taking antiretroviral regimens consisting of 2 or more pills per day. Although causality could not be assessed, I found the demonstrated association in this study quite compelling. One caveat is that this study was performed in insured patients. It will be important that similar analyses are performed in other populations of patients such as those receiving Medicaid. In addition, I hope that future analyses will address cost-effectiveness of the once-daily fixed-dose combination pills.

HIV testing behaviors

Editors’ Commentary

that overall, a large proportion of Americans are still not accessing HIV testing. Du et al suggest a lack of access to health care is associated with lack of access to HIV testing. It is critical that innovative methods be designed that provide access to HIV testing in all persons. Perhaps we should learn from effective home-based HIV testing programs in Africa that have provided HIV testing to large numbers of people. For example, one home-based HIV counseling and testing program in Kenya was able to reach a large proportion over a short period of time; specifically, 105,859 individuals representing 93% of the eligible population were provided HIV counseling and testing over a period of 7 months. Use of oral fluid for HIV rapid testing is generally easier than procuring blood via finger stick or phlebotomy. Results from studies of false-positive oral fluid rapid tests have led to some testing programs to switch from oral fluid to blood for HIV testing. Therefore, it is very reassuring that in the meta-analysis of 25 studies presented by Balram et al, oral fluid testing performance characteristics were very similar to those of rapid HIV tests (using finger stick blood). Critical to accurate HIV rapid testing (using either oral fluid or blood) is effective training of HIV testers as well as ongoing quality control.
HIV testing behaviors and rapid testing technology

In an attempt to assess the impact of the Centers for Disease Control and Prevention (CDC) 2006 recommendation for opt-out HIV testing in health care settings for all persons aged 13-64 years, investigators from Penn State University College of Medicine analyzed survey results to assess HIV testing experiences among a nationally representative group of adults 18 years and older. A second study, also presented at IDSA 2010, evaluated the accuracy of the oral-swab rapid HIV test in comparison with finger-stick tests. An analysis of data from the Behavioral Risk Factors Surveillance System (BRFSS), a nationally representative telephone survey of US adults 18 years and older that includes questions about HIV testing, included data from 284,688 adults who were asked about HIV testing in 2008, with a small increase in the proportion of those reporting they were ever tested for HIV (to 58.7%). The investigators, who presented their findings at IDSA 2010, found that among individuals younger than 44 years, women were more likely to be tested than men. In addition, testing was positively associated with minority race, being single, and having a college education, among other factors. Factors that were negatively associated with testing included living in a rural area (adjusted odds ratio [aOR] = 0.87; P < .01), lack of routine medical checkups in the past 5 years (aOR = 0.77; P < .01), and residing in a state with opt-in HIV testing policies (aOR = 0.93; P = .03). The investigators recommended that legislative barriers to HIV testing should be reduced if the CDC’s recommendations for HIV testing are to be implemented.

HIV testing comparison demonstrates accuracy of oral HIV test. The results of a meta-analysis of published data from 25 studies of OraQuick® oral and OraQuick® finger-stick HIV tests found that the oral tests were slightly less sensitive but equally specific as the finger-stick test. Given the reported preference of patients for the oral test, the data provide support for its use in more testing settings. The studies included in the analysis were divided into three groups: those that offered within-study head-to-head comparisons of oral mucosal transudate (OMT) and finger-stick blood (FSB) tests, those that looked at OraQuick OMT samples only, and those analyzing OraQuick FSB samples only. The results were evaluated according to the test type.

According to the analyses, the sensitivity and specificity estimates varied across studies. In the pooled analyses, with all factors being equal, the sensitivity of the oral test was slightly lower than the finger-stick test, while the specificity was slightly higher with the oral test (Table 5). The 95% confidence intervals showed significant overlap. They investigated concluded that the performance of the two tests was comparable and that both tests are appropriate for use in HIV screening initiatives in the United States and abroad.

Table 5. Results of bivariate regression: sensitivity and specificity across select subgroups (n > 4)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Pooled Sensitivity</th>
<th>Pooled Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subgroup 1a: OMT (within study) (n = 8)</td>
<td>97.99% (95% CI 94.85, 99.23)</td>
<td>99.76% (95% CI 99.48, 99.89)</td>
</tr>
<tr>
<td>Subgroup 1b: FSB (within study) (n = 8)</td>
<td>99.53% (95% CI 96.88, 99.93)</td>
<td>99.91% (95% CI 99.84, 99.95)</td>
</tr>
<tr>
<td>Subgroup 2: OMT (n = 6)</td>
<td>99.43% (95% CI 95.28, 99.94)</td>
<td>99.86% (95% CI 99.22, 99.98)</td>
</tr>
<tr>
<td>Subgroup 3: FSB (n = 11)</td>
<td>99.65% (95% CI 98.88, 99.89)</td>
<td>99.69% (95% CI 99.11, 99.89)</td>
</tr>
</tbody>
</table>

CI, confidence interval; FSB, finger-stick blood; OMT, oral mucosal transudate.


Editors’ Commentary

Dr Sax: With respect to testing behaviors among adults, I was surprised to see this result. I wonder whether that is an indication that we have reduced the number of people who haven’t been tested, or if there is some increased complacency about it. I think it was significant that being in a state that has opt-in policies means you are less likely to be tested for HIV. That is something that we feel very strongly about in Massachusetts.

The key thing about rapid testing, at least based on the rapid tests that are available in the United States, is that the test performance can only be considered as good as the first step in our usual HIV testing algorithm (the ELISA). It is quite sensitive, whether you use the oral or the finger-stick test, but the confirmatory step is still very critical. Overall, these results are reassuring about the use of oral fluid testing for HIV screening, as long as the people who do it understand both the strengths and limitations of this rapid test. One of the things that we look forward to is an advance in rapid testing such that it would provide a test performance that is comparable to our usual testing algorithm.

Dr Hodder: The National Health Interview Survey has demonstrated that since the CDC’s recommendation for opt-out testing in 2006, 8.7 million more Americans have been tested for HIV. Nonetheless, the recently presented data suggest...