The AMERICAN ACADEMY of HIV MEDICINE

HIV SPECIALIST

PATIENT CARE, PRACTICE MANAGEMENT & PROFESSIONAL DEVELOPMENT INFORMATION for HIV CARE PROVIDERS

Summer 2011

www.aahivm.org

The Evolving Dynamic of CARE

New Research Continues to Change How We Treat HIV

Treatment = Prevention

CDC Exclusive: Stopping the Spread

Research Updates

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A surge of evidence supports treating HIV earlier

- 2011 DHHS guidelines:
  - HAART is recommended for patients with a CD4 cell count of 350–500 cells/mm³
  - Half of the Panel favors initiating HAART for patients with a CD4 cell count >500 cells/mm³, while the remainder views HAART as an option
  - As part of the consideration for earlier initiation of HAART, the Panel cites both the benefits and potential limitations
- Significant improvement in patient survival
- Better long-term CD4 cell count
- Significant reduction in the probability of morbidity
- Lower probability of HIV transmission

Talk to your patients and help them understand the potential of earlier initiation of HAART.

DHHS = Department of Health and Human Services.

*69% increase in relative risk of death when treatment was deferred until CD4 cell count was ≤500 cells/mm³ (versus initiating at 351–500 cells/mm³; P<0.001) and 94% increase in relative risk of death when treatment was deferred until CD4 cell count was ≤500 cells/mm³ (versus initiating at >500 cells/mm³; P<0.0001), based on the NA-ACCORD analysis.²

*After 6 years, patients with a baseline CD4 cell count >550 cells/mm³ achieved and maintained nearly normal CD4 levels with HAART (versus <350 cells/mm³) in an observational analysis.

*Earlier initiation (>350 cells/mm³) was associated with significantly reduced probability of opportunistic disease (OD), serious non-ADIS events, and non-OD deaths in an analysis of the SMART study.*
AAHIVM has partnered with the Institute for Technology in Health Care to create the AAHIVM/Institute for Technology in Health Care HIV Practice Award. Two $10,000 awards will be presented to a person(s) who has created, adapted and/or used innovative technology in their HIV practice and is willing to share that technology with others to improve patient care.

To learn more about the criteria and how to submit your practice for consideration, visit our website at www.aahivm.org or go to page 26 for more details.
AFTER MANY WEEKS of heated, divisive debate, the Federal Government agreed to a budget deal that raised the debt limit and cut trillions from the Federal budget. While the debt limit crisis has been resolved for now, the true impact of the funding cuts to major health programs will be felt by our Members and our patients for years to come.

We all know there is almost always some fat in any budget—whether it is research or practice. But if you ask anyone in HIV care, they will agree that fat is gone. Certainly as well, so are the days of “doing more with less.” The future holds the specter of doing less with less—and that translates into lost research opportunities and unnecessarily lost lives on the treatment side of the ledger.

In September of 2009, AAHIVM Board of Director Chair Dr. Donna Sweet testified before the US House of Representatives Committee on Energy and Commerce on the reauthorization of the Ryan White Program. In her testimony she said the following:

“The HIV Program KU Internal Medi-

The Limits of Doing More with Less

cine Midtown provides care and treatment to 1246 patients as of today. Of these, 40 percent would have no coverage if it were not for the Ryan White Care Act. To broadly paint the picture: In the last 10 years my clinic’s patient load has doubled, and my funding has remained the same. To supplement our insufficient federal dollars, we will often do things like annual bake sales and picnics to help raise money for the clinic and its patients. Even though we are committed to do things like this to keep the clinic afloat, it is hard to believe that we have to resort to girl-scout-styled fundraising to care for the sick in a country like ours.”

This issue of HIV Specialist focuses on the future of HIV care, including a look at the pipeline for both public and private HIV research. While the coming pages are full of promising treatment advances, if funding continues to deteriorate it will have a potentially negative impact on HIV research in years to come.

A recent Issue Brief published by amFAR and the Treatment Action Group (July 2011), spoke about the broad health and economic benefits of HIV research not only for HIV, but for a variety of other diseases (including cancer, heart disease, osteoporosis and hepatitis). But it also noted that “For AIDS research, flat funding has resulted in an 18 percent decline in NIH’s ability to support new research grants.” And this is before any of the proposed trillion(s) of dollars in cuts over the coming decade.

Heath Care Reform, if fully implemented, should help on the practice side, but there is no comparable savior for HIV research on the horizon. As you well know, much of the progress in treating HIV patients over the past 25 years has come through our investment in research. HIV research has been one of the most productive areas of biomedical research over the past two decades, with tens of thousands of lives saved in the U.S. and around the world.

We need to work with our public and private colleagues and with Congress to protect this portfolio of HIV research grants. Once they are gone—or greatly diminished—our talented researchers will be forced to shift their focus to other disease areas. As this brain drain occurs, the progress we have made in treating HIV and ultimately the hope for a cure will also fade.
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ON THE COVER: Zoila Angeles, Medical Laboratory Scientist, is shown at work at the UCSF AIDS Research Institute Laboratory of Clinical Virology at San Francisco General Hospital. Photo by Teri Liegler.
Young Gay Blacks: the Crisis Continues

THE NATIONAL ASSOCIATION OF PEOPLE WITH AIDS (NAPWA) and I personally salute the CDC for reporting in early August what we all already guessed: the number of new HIV infections is level for the country as a whole, but is steadily rising in young gay Black men.

Tom Frieden (Thomas R. Frieden, MD, MPH Director, CDC Administrator, Agency for Toxic Substances and Disease Registry) spoke for all of us when he said, “We’re very concerned about this trend.” As an openly gay Black man who has lived with HIV for 22 years and seen friends and partners die, I wholeheartedly agree: we have to change this.

Studies show that young gay Black men are at least as likely to use condoms as their non-Black peers, so we cannot blame the rapid spread of HIV among them on riskier behavior. On the contrary: it is driven by the high number of young gay Black men already infected and the high number of them who do not know they are infected. The special impact of HIV on these young people is caused by structural issues in American society that mainstream politicians and the press don’t like to talk about—especially in this Tea Party-driven political climate.

Structural issues are always hard to talk about. Poverty and prejudice are harder than any. But let’s face facts: HIV’s disproportionate impact on African-Americans and other Americans of color is the price this country pays for letting color mean poverty, and poverty mean substandard healthcare and health literacy.

And HIV’s disproportionate impact on young gay men has everything to do with stigma and homophobia, which discourage young men from learning their status and seeking treatment. Let those two problems come together and you have the perfect storm.

We need to address unequal economic and educational opportunity, which keep poor people poor, but that will be a generation’s work. In the meantime, all lower-income Americans, White and Black, straight and gay, need fairer access to healthcare and support services.

Achieving that, in this political climate, means driving home relentlessly the objective truth that three-quarters of HIV-related healthcare costs are borne in the public sector, and it costs the public less to test aggressively and treat early than to do nothing and let more people get sick. Our best defense in the coming deficit reduction negotiations is a good offense: it costs more to do less, and we can prove it.

We need to address stigma, too, and Washington is not the only place we have to do that – although repeal of Don’t Ask, Don’t Tell was a great step forward, and we look forward to an eventual Supreme Court decision throwing out the Defense of Marriage Act.

We also need to work with faith groups and leaders in communities that have traditionally been unfriendly to same-sex sexuality, to spread the word that it’s more important to save the lives of a generation of young Black men than it is to worry about what they do in bed.

And we need to work with those who have been the target of stigma and don’t want to hear what anyone else has to say about their intimate lives unless it comes from a very trusted source. Our Washington, DC-based Bayard Rustin Project trains openly gay, openly positive young Black men to do outreach in their own social networks, spreading the word about risk awareness and the need to get tested more often than people in less heavily infected populations, and helping those who test positive navigate the healthcare system to find the treatment and services they need.

The great promise of expanded testing, especially in groups that already have a high incidence of infection, is that most people who learn they are positive change their behavior to protect others, and people who are in treatment with undetectable viral load are less likely to infect others, even when their safer behavior sometimes lapses.

Young gay Black men who already live with HIV are uniquely qualified to reach their at-risk peers with the Take the Test, Take Control message. The Bayard Rustin Project is working among D.C.’s young gay Black men, and it should be a model for peer outreach across the country.

The CDC report is a call to action. We lost a generation of young men in the first 15 years of this epidemic. I was there. I saw it. We can’t let it happen again.

ABOUT THE AUTHOR: Frank J. Oldham, Jr. is President and CEO of the National Association of People With AIDS.
ATRIPLA became the first FDA-approved Single Tablet Regimen*

For adults with HIV-1: one tablet, once daily, alone or in combination, on an empty stomach, preferably at bedtime¹

ATRIPLA is the #1 prescribed treatment regimen for HIV-1²

INDICATION

• ATRIPLA is indicated for use alone as a complete regimen or in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults.

IMPORTANT SAFETY INFORMATION

WARNINGS: LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS and POST-TREATMENT EXACERBATION OF HEPATITIS B

• Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including tenofovir disoproxil fumarate (DF), a component of ATRIPLA, in combination with other antiretrovirals.

• ATRIPLA is not approved for the treatment of chronic hepatitis B virus (HBV) infection, and the safety and efficacy of ATRIPLA have not been established in patients coinfected with HBV and HIV-1. Severe acute exacerbations of hepatitis B have been reported in patients who have discontinued EMTRIVA® (emtricitabine) or VIREAD® (tenofovir DF), which are components of ATRIPLA. If appropriate, initiation of anti-hepatitis B therapy may be warranted.


Please see Important Safety Information, including Boxed WARNINGS, for ATRIPLA and brief summary of Full Prescribing Information on adjacent pages.
Contraindications

- ATRIPLA is contraindicated in patients with previously demonstrated clinically significant hypersensitivity (e.g., Stevens-Johnson syndrome, erythema multiforme, or toxic skin eruptions) to efavirenz, a component of ATRIPLA.

- Coadministration of ATRIPLA with beprilid, cisapride, midazolam, pimozone, triazolam, or ergot derivatives is contraindicated, since competition for CYP3A by efavirenz could result in inhibition of metabolism of these drugs and create the potential for serious and/or life-threatening adverse reactions.

- Concomitant use of ATRIPLA with voriconazole, atazanavir (with or without ritonavir), St. John’s wort (Hypericum perforatum) or St. John’s wort-containing products is not recommended.

Warnings and Precautions

Coadministration with Related Products

- Since ATRIPLA contains efavirenz, emtricitabine, and tenofovir DF, ATRIPLA should not be coadministered with SUSTIVA® (efavirenz), EMTRIVA, VIREAD, or TRUVADA® (emtricitabine/tenofovir DF). Due to similarities between emtricitabine and lamivudine, ATRIPLA should not be coadministered with drugs containing lamivudine, including Combivir® (lamivudine/zidovudine), Epivir® or Epivir-HBV® (lamivudine), Epzicom® (abacavir sulfate/lamivudine), or Trizivir® (abacavir sulfate/lamivudine/zidovudine).

- ATRIPLA should not be administered with HEPSERA® (adefovir dipivoxil).

Psychiatric Symptoms

- Serious psychiatric adverse experiences, including severe depression (2.4%), suicidal ideation (0.7%), nonfatal suicide attempts (0.5%), aggressive behavior (0.4%), paranoid reactions (0.4%), and manic reactions (0.2%), have been reported in patients receiving efavirenz. In addition to efavirenz, factors identified in a clinical study that were associated with an increase in psychiatric symptoms included a history of injection drug use, psychiatric history, and use of psychiatric medication. There have been occasional reports of suicide, delusions, and psychosis-like behavior, but it could not be determined if efavirenz was the cause. Patients with serious psychiatric adverse experiences should be evaluated immediately to determine whether the risks of continued therapy outweigh the benefits.

Nervous System Symptoms

- Fifty-three percent of subjects reported central nervous system symptoms (including dizziness [28.1%], insomnia [16.3%], impaired concentration [8.3%], somnolence [7.0%], abnormal dreams [6.2%], and hallucinations [1.2%]) when taking efavirenz compared to 25% of subjects receiving placebo. These symptoms usually begin during Days 1-2 of therapy and generally resolve after the first 2-4 weeks of therapy; they were severe in 2.0% of subjects, and 2.1% of subjects discontinued therapy. After 4 weeks of therapy, the prevalence of nervous system symptoms of at least moderate severity ranged from 5% to 9% in subjects treated with regimens containing efavirenz. Nervous system symptoms are not predictive of the less frequent psychiatric symptoms.

New Onset or Worsening Renal Impairment

- It is recommended that creatinine clearance (CrCl) be calculated in all patients prior to initiating therapy and as clinically appropriate during therapy with ATRIPLA, and routine monitoring of CrCl and serum phosphorus be performed for patients at risk of renal impairment, including patients who have previously experienced renal events while receiving adefovir dipivoxil. ATRIPLA should not be given to patients with CrCl <50 mL/min. Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported with the use of tenofovir DF. ATRIPLA should be avoided with concurrent or recent use of a nephrotoxic agent.

Reproductive Risk Potential

- ATRIPLA may cause fetal harm when administered during the first trimester to a pregnant woman. Women should not become pregnant or breastfeed while taking ATRIPLA. Barrier contraception must always be used in combination with other methods of contraception (eg, oral or other hormonal contraceptives). Because of the long half-life of efavirenz, adequate contraceptive measures are recommended for 12 weeks after discontinuation of ATRIPLA. If the patient becomes pregnant while taking ATRIPLA, she should be apprised of the potential harm to the fetus.

Rash

- Mild-to-moderate rash is a common side effect of efavirenz. In controlled clinical trials, 26% of subjects treated with efavirenz experienced new-onset skin rash compared with 17% of subjects treated in control groups. ATRIPLA should be discontinued in patients developing severe rash associated with blistering, desquamation, mucosal involvement, or fever.

Hepatotoxicity

- Liver enzymes should be monitored before and during treatment in patients with underlying hepatic disease, including hepatitis B or C infection; in patients with marked transaminase elevations; and when ATRIPLA is administered with ritonavir or other medications associated with liver toxicity. A few of the postmarketing reports of hepatic failure, including cases in patients with no pre-existing hepatic disease or other identifiable risk factors, were characterized by a fulminant course, progressing in some cases to transplantation or death. Liver enzyme monitoring should be considered for patients without pre-existing hepatic dysfunction or other risk factors.

Decreases in Bone Mineral Density

- Bone mineral density (BMD) monitoring should be considered for patients who have a history of pathologic bone fracture or are at risk for osteoporosis. Decreases in BMD have been seen with tenofovir DF. Cases of osteomalacia (associated with proximal renal tubulopathy and which may contribute to fractures) have been reported in association with the use of tenofovir DF.

Seizure

- Use ATRIPLA with caution in patients with a history of seizures. Convulsions have been observed in patients receiving efavirenz, generally in the presence of known medical history of seizures.

Immune Reconstitution Syndrome

- Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including the components of ATRIPLA.

Fat Redistribution

- Redistribution/accumulation of body fat has been observed in patients receiving ATRIPLA.

Adverse Reactions

- In Study 934, through 144 weeks, the most frequently reported Grades 2-4 adverse reactions reported in ≥5% of subjects receiving efavirenz + emtricitabine + tenofovir DF were diarrhea (8%), nausea (8%), headache (7%), insomnia (6%), anxiety (5%), and nasopharyngitis (5%). The most common adverse reactions (incidence ≥10%, any severity) occurring in Study 934 include diarrhea, nausea, fatigue, headache, dizziness, depression, insomnia, abnormal dreams, and rash.

Drug Interactions

- Coadministration of ATRIPLA with didanosine should be undertaken with caution. Patients receiving this combination should be monitored closely for didanosine-associated adverse reactions.

- Lopinavir/ritonavir has been shown to increase tenofovir concentrations. Patients on lopinavir/ritonavir should be monitored closely for didanosine-associated adverse reactions.

- Coadministration of ATRIPLA and atazanavir is not recommended. Efavirenz and tenofovir DF have been shown to decrease concentrations of atazanavir. Atazanavir has also been shown to increase tenofovir concentrations.

- Saquinavir should not be used as the only protease inhibitor in combination with ATRIPLA.

See Full Prescribing Information for complete list of drug-drug interactions.

Hepatic Impairment

- ATRIPLA is not recommended for patients with moderate or severe hepatic impairment because of insufficient data; use caution in patients with mild hepatic impairment.

Dosage and Administration

- The dose of ATRIPLA is 1 tablet (containing 600 mg of efavirenz, 200 mg of emtricitabine, and 300 mg of tenofovir DF) once daily taken orally on an empty stomach. Dosing at bedtime may improve the tolerability of nervous system symptoms. ATRIPLA is not recommended for use in patients with CrCl <50 mL/min.
ATRIPLÁ® (efavirenz 600 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg) Tablets

Brief Summary of Prescribing Information. For complete prescribing information consult official package insert.

INDICATIONS AND USAGE
ATRIPLÁ® (efavirenz 600 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg) is indicated for use as a complete regimen or in combination with other antiretroviral drugs for the treatment of HIV-1 infection in adults.

CONTRAINDICATIONS
ATRIPLÁ® is contraindicated in patients with previously documented severe hepatic steatosis, with fatal cases, have been reported with the use of nucleoside analogs including tenofovir DF, a component of ATRIPLÁ, in combination with other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering nucleoside analogs to any patient with liver disease. Liver function should be monitored closely in patients with no known risk factors.

ATRIPLÁ® should not be coadministered with ritonavir-boosted atazanavir (atazanavir/ritonavir) or atazanavir. Concurrent administration of ATRIPLÁ® with atazanavir/ritonavir could result in severe hyperbilirubinemia, hepatic failure, or both.

ATRIPLÁ® should be used with caution in patients taking concomitant medications that are substrates or inhibitors of CYP3A4. Coadministration of antifungal agents with voriconazole and ATRIPLÁ® has been associated with severe hepatic failure. Use of ATRIPLÁ® in these patients is not recommended. Patients with active liver disease, including hepatitis B or C infection; patients with marked transaminase elevations; and patients treated with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors.

ATRIPLÁ® should be initiated with caution in patients who are at risk for or have documented HLA-B*5701. A causal relationship has not been established.

DOSAGE AND ADMINISTRATION
Patients receiving ATRIPLÁ should be alerted to the potential for additive effects from concomitant medications. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering nucleoside analogs to any patient with liver disease. Liver function should be monitored closely in patients with no known risk factors.

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PATIENT COUNSELING INFORMATION and FDA-APPROVED PATIENT LABELING
HIV-1 to others through sexual contact or blood contamination; patients should be advised to continue to practice safer sex and to take the drug as prescribed. ATRIPLÁ® is not approved for the treatment of chronic HBV infection, and it is recommended that all patients with HIV-1 be tested for the presence of HBV.

EFFECTS ON LABORATORY TESTS
Blood chemistry abnormalities include increases in creatinine, bilirubin, and AST/ALT. Rarely, decreases in creatinine clearance have been observed.

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Emtricitabine - No postmarketing adverse reactions have been identified for inclusion in this section.

Nucleoside analogs: Hematologic and/or serious non-hematologic adverse reactions may occur. Changes in mean hematologic values include anemia, neutropenia, leukopenia, thrombocytopenia, lymphopenia, and eosinophilia. Changes in mean non-hematologic values include rash, hyperglycemia, proteinuria, pruritus, increased transaminase levels, and akathisia. Other changes have included altered liver and renal function, acne, decreased weight, nausea, vomiting, constipation, neuralgiaplexus, paresthesia, headache, asthenia, diarrhea, respiratory tract infections, and urinary tract infections. Some patients accidentally taking 600 mg twice daily have reported increased nervous system symptoms. One patient reported a change in behavior and mood following accidental overdose of 1000 mg twice daily for 3 months. The patient was first treated with benzodiazepines and then titrated to lorazepam.

Narcotic analgesics — Methadone: Methadone concentration. Co-administration of efavirenz in HIV-infected individuals receiving methadone may result in increased plasma levels of methadone, and may lead to adverse events associated with increased methadone concentrations. Methadone plasma levels were increased by 20% to 25% in patients co-administered with efavirenz and methadone. In vitro studies demonstrated a minimal interaction of efavirenz on methadone plasma concentrations. Administration of methadone to patients co-administered with efavirenz should be undertaken with caution and patients receiving this combination should be monitored closely for signs of toxicity associated with increased methadone concentrations. Methadone should be dose decreased in patients who develop dose-dependent adverse reactions. Dose adjustments for methadone should be small because of the relatively short half-life of methadone. Daily methadone dose should be divided into 2 or 3 small doses, with at least 2 hours between dosing. Substitution of a full course of withdrawal should then be applied as necessary.

**Please see Full Prescribing Information (Table 4) for additional information; this list is not inclusive.

USE IN SPECIFIC POPULATIONS

Pregnancy (Category D) [See Warnings and Precautions]

Nursing Mothers: The Centers for Disease Control and Prevention recommend that HIV-1 infected mothers not breastfeed their infants to avoid risking transmission of HIV-1. Studies in rhesus monkeys demonstrated that both human milk and HIV-1 were secreted in human milk. Because of both the potential for HIV-1 transmission and the potential for serious adverse reactions in nursing mothers, nursing mothers should not breastfeed if they are receiving ATRIPLA (emtricitabine 600 mg; efavirenz 600 mg; tenofovir disoproxil fumarate 300 mg).

Pediatric Use: ATRIPLA is not recommended for patients less than 15 years of age because it is a fixed-dose combination of three drugs with established safety and effectiveness profiles in adults.

Geriatric Use: Clinical studies of efavirenz, emtricitabine, or tenofovir did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. In general, dose selection for the elderly should be cautious, starting with the lower end of the recommended dose.

OVERDOSAGE

If overdose occurs, the patient should be monitored for evidence of toxicity, including monitoring of vital signs and observation of behavior. charcoal or other means of gastrointestinal decontamination should not be used, since efavirenz is not absorbed from the gastrointestinal tract. An adequate amount of activated charcoal may be administered to an emaciated or dehydrated patient. Activated charcoal is unlikely to be effective in the treatment of an overdose in a normal-weight, healthy patient. There is no specific antidote for treatment of an overdose. The patient should be treated symptomatically and supportive care should be administered. If indicated, specific treatment of emergencies associated with the use of each of the active components may be considered.

DRUG INTERACTIONS

Efavirenz is a potent inducer of the cytochrome P450 3A4 (CYP3A4) isozyme. Administration of concomitant drugs that are metabolized by CYP3A4 can result in decreased plasma concentrations of efavirenz. Administration of efavirenz with drugs primarily metabolized by these isozymes may result in altered plasma concentrations of the CYP3A4 substrates. In contrast, concomitant administration of other drugs, such as nelfinavir, with efavirenz may result in increased plasma concentrations of efavirenz. In general, concomitant administration of other antiretroviral agents, in particular those that induce CYP3A4 or CYP2C19, should be avoided unless the potential benefit of coadministration outweighs the risk of reduced antiretroviral efficacy. Concomitant administration of efavirenz with other drugs that prolong the QT interval, such as the antiarrhythmic drugs encainide, flecainide, propafenone, or quinidine, should be avoided. In addition, use of 5-hydroxytryptamine 2A/2C receptor antagonists, such as domperidone, has resulted in QT prolongation in a small number of patients. Co-administration of efavirenz with drugs that are potent inhibitors of CYP3A4, such as clarithromycin, ketoconazole, indinavir, ritonavir, and fosamprenavir, may result in increased plasma concentrations of these inhibitors and, in some cases, in toxicity. In addition, concomitant use of efavirenz with drugs that are weak inhibitors of the cytochrome P450 3A4 (CYP3A4) isozyme, such as amiodarone, azithromycin, atorvastatin, clarithromycin, diazepam, fluconazole, fluoxetine, indinavir, itraconazole, ketoconazole, maraviroc, methadone, nelfinavir, nefazodone, nateglinide, olmesartan, pantoprazole, propafenone, ranolazine, ritonavir, and saquinavir, may result in increased plasma concentrations of efavirenz.

Coadministration of tenofovir DF and emtricitabine will be undertaken with caution and patients receiving this combination should be monitored closely for dose response and clinical response and may require dose reduction. Patients with moderate or severe hepatic impairment are at increased risk for lactic acidosis, and should have careful monitoring whenever efavirenz is co-administered. In a study of patients with moderate or severe hepatic impairment, there were insufficient data to support dose reductions. Dose adjustments for atazanavir should be undertaken with caution and patients receiving atazanavir should be monitored for signs of toxicity.

Coadministration of atazanavir with tenofovir DF is not recommended. Coadministration of atazanavir with efavirenz or tenofovir DF is not recommended. Coadministration of atazanavir with ritonavir may result in increased plasma concentrations of efavirenz and tenofovir DF. In vitro studies have demonstrated that efavirenz inhibits CYP3A4, CYP2D6, and CYP2C19 and, therefore, coinhibition of these enzymes may be expected if a patient is taking a substance that is a substrate of one or more of these enzymes when concomitantly receiving efavirenz. As a result, dose reductions of these active components may be necessary.

Coadministration of efavirenz, emtricitabine, and tenofovir DF is not recommended. Coadministration of efavirenz with efavirenz or tenofovir is not recommended. Coadministration of efavirenz with atazanavir is not recommended. Coadministration of efavirenz with atazanavir plus ritonavir is not recommended. Coadministration of efavirenz with efavirenz or tenofovir should be avoided unless the potential benefit of coadministration outweighs the risk of reduced antiretroviral efficacy. In general, concomitant administration of other antiretroviral agents, in particular those that inhibit CYP3A4 or CYP2C19, should be avoided unless the potential benefit of coadministration outweighs the risk of reduced antiretroviral efficacy. Concomitant administration of efavirenz with other drugs that prolong the QT interval, such as the antiarrhythmic drugs encainide, flecainide, propafenone, or quinidine, should be avoided. In addition, use of 5-hydroxytryptamine 2A/2C receptor antagonists, such as domperidone, has resulted in QT prolongation in a small number of patients. Co-administration of efavirenz with drugs that are potent inhibitors of CYP3A4, such as clarithromycin, ketoconazole, indinavir, ritonavir, and fosamprenavir, may result in increased plasma concentrations of these inhibitors and, in some cases, in toxicity. In addition, concomitant use of efavirenz with drugs that are weak inhibitors of the cytochrome P450 3A4 (CYP3A4) isozyme, such as amiodarone, azithromycin, atorvastatin, clarithromycin, diazepam, fluconazole, fluoxetine, indinavir, itraconazole, ketoconazole, maraviroc, methadone, nelfinavir, nefazodone, nateglinide, olmesartan, pantoprazole, propafenone, ranolazine, ritonavir, and saquinavir, may result in increased plasma concentrations of efavirenz.

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Myron Cohen, MD, professor of medicine at the University of North Carolina School of Medicine
HE SCIENTIFIC EVIDENCE IS MOUNTING that early treatment of those infected with HIV with combination antiretroviral therapy (cART) can dramatically reduce the transmission of the virus to their uninfected partners. Several new studies published so far this year provide evidence that treatment, indeed, is a key to prevention.

The findings can be expected to significantly affect the approach of many HIV practitioners as they care for their patients.

“I think we will embrace much earlier treatment,” said Myron Cohen, MD, professor of medicine at the University of North Carolina School of Medicine, and principal investigator of the HIV Prevention Trials Network (HPTN) 052 study reported in May.

That study found that early treatment of HIV-infected people with cART led to a 96 percent reduction in transmission of the virus to their uninfected partners. Funded by the National Institute of Allergy and Infectious Diseases (NIAID) at the National Institutes of Health (NIH), the study was designed to evaluate whether early versus delayed use of cART by HIV-infected individuals would reduce transmission of HIV to their uninfected partners and benefit the HIV-infected individual as well.

“HPTN 052 is the first randomized clinical trial to indicate definitively that an HIV-infected individual can reduce sexual transmission to an uninfected partner by beginning antiretroviral therapy sooner,” said Dr. Cohen, who directs the Institute of Global Health & Infectious Diseases at UNC.

“We could not be more pleased that the World Health Organization (WHO) is considering these findings in its work on guidance for serodiscordant couples.”

In fact, the findings of this and two other studies that were presented at the International AIDS Conference in Rome in July prompted WHO to delay publishing its long-awaited guidelines for serodiscordant heterosexual couples.

HPTN 052 was conducted at 13 sites in Botswana, Brazil, India, Kenya, Malawi, South Africa, Thailand, the United States and Zimbabwe. (Details were discussed in the Spring 2011 edition of HIV Specialist, which can be found at www.aahivm.org.) Initial trial results were published July 18 in The New England Journal of Medicine.

“052 demonstrates remarkable potency of ART to prevent HIV transmission,” Dr. Cohen told HIV Specialist. “But it is a proof of a biological concept. People need to be tested, treated well, and take their pills, as the participants did in the study for the strategy to be effective at a population level.”

The Botswana Study
Meanwhile, TDF2, another study by CDC that was conducted in partnership with the Botswana Ministry of Health, found that a once-daily tablet containing tenofovir disoproxil fumarate and emtricitabine (TD/FTC), reduced the risk of acquiring HIV infection by about 63 percent overall in the study population of uninfected heterosexual men and women.

A total of 1,219 HIV-uninfected heterosexual male and female HIV negative participants (aged 18-39) in Botswana were enrolled in the TDF2 trial and randomly assigned to take a daily TD/FTC pill or a placebo pill. All participants were provided comprehensive HIV prevention services, including male and female condoms, intensive risk-reduction behavioral counseling, and testing and treatment for sexually transmitted infections. Of the participants 54.7 percent were male, 45.3 percent female.

In the primary analysis, among the 601 participants who received TDF/FTC, there were nine who became infected
As the impact of this research begins to be felt and as pressures mount to begin treatment earlier and to include uninfected partners in some instances, the question of funding is bound to move into the forefront of discussion and debate.

with HIV during the study. Among the 599 individuals who received a placebo, 24 became infected with HIV during the study—an overall relative risk reduction of 62.6 percent. Limiting the data analysis to participants on TDF/FTC when infected, the protected efficacy was even greater at 77.9 percent.

Consistent with other PrEP studies, preliminary analyses did not identify any significant safety concerns associated with daily use of TDF/FTC. Participants assigned to receive the study drug were more likely than those assigned to the placebo arm to report nausea, vomiting, and dizziness, but there were no differences in serious adverse events between the treatment and placebo arms.

“Given the severity of the HIV epidemic among heterosexual men and women globally—and the critical need for female-controlled prevention methods—this study provides exciting and welcome news,” said Jonathan Mermin, M.D., director of CDC’s Division of HIV/AIDS Prevention. “The next important step is to fully review the data and assess when and how PrEP should best be used for HIV prevention among heterosexuals.”

**Partners PrEP**

The University of Washington (UW) released preliminary results of additional research, the Partners PrEP study, which also found that daily PrEP reduced HIV transmission among heterosexual couples in Kenya and Uganda.

That study found that two separate antiretroviral regimens—tenofovir and TDF/FTC—significantly reduced HIV transmission among serodiscordant couples. The findings were released after the trial’s independent data safety monitoring board conducted an interim review of the trial data and recommended that the study be stopped early due to strong evidence of effectiveness.

In this study, 5,758 serodiscordant couples were recruited from nine locations beginning in July 2008. The uninfected partners were randomly assigned to take the medications or a placebo and all were counseled on how to avoid infection and were provided condoms.

Through the end of May 2011, there had been 47 infections among those taking the placebo, while only 18 in those taking tenofovir (a 62 percent reduction) and 13 in those taking TDF/FTC (a reduction of 73 percent). Both men and women were equally protected.

“These results are fundamentally important for HIV prevention, especially in Africa,” Jared Baeten, M.D., a physician at the University of Washington who co-directed the Kenya and Uganda study, told *The Washington Post.*

“Our biggest challenge now is how do we move from research to getting things out to the general public where they’re most needed,” Lynn Paxton, an epidemiologist at the Centers for Disease Control and Prevention, who led the Botswana study, told *The Post.*

The results of those studies were in sharp contrast to the FEM-PrEP study reported earlier this year, in which 2,000 women in Kenya, Zimbabwe and South Africa took TDF/FTC or placebo. That study showed little preventive benefit from the drug, and since then experts have suggested study participants most likely had poor adherence to the study drugs.

Dr. Baeten pointed out that in his study participants took their medication 97 percent of the time. The CDC study in Botswana reported adherence rate of 84 percent.

“I think adherence is the biggest driver of the difference between our study and theirs,” he commented.

**Investment Value**

As the impact of this research begins to be felt and as pressures mount to begin treatment earlier and to include uninfected partners in some instances, the question of funding is bound to move into the forefront of discussion and debate.

Ambassador Eric Goosby, U.S. Global AIDS Coordinator, pointed out in a July 18 blog that last summer the CAPRISA study, funded by the U.S. President’s Emergency Plan for AIDS Relief (PEPFAR) of a tenofovir-based microbicide demonstrated successful proof-of-concept for this female controlled prevention method.

The study, he noted, showed that women using the microbicide gel had an average of 39 percent fewer HIV infections and 51 percent fewer genital herpes infections compared to women who used a placebo gel.

“The results of this study were clear evidence of the importance of U.S. investments—across multiple agencies—in microbicides,” he said. “And through PEPFAR, our country teams will be working to create the regulatory path and client demand for these products when they are ready to be marketed, so that innovation can be quickly brought to bear in order to save lives.”

These latest studies with their implications for prevention have created “a mood of optimism and promise,” he said, adding that many of these advances have benefited from the funding and expertise found within the U.S. government.

Dr. Cohen said he believes the results of the 052 study that he helped lead are evidence of the value of the investment in research and in medications used for prevention.

“I believe the results will speak for themselves in terms of clinical benefit and HIV cases averted,” he said. “Pay less now or much more later.”

**HIV**

**ABOUT THE AUTHOR:** Editor of HIV Specialist, Bob Gatty is a Washington, DC-area health policy writer and publications professional. He is founder of G-Net Strategic Communications and can be reached at bob@gattyedits.com.
A NEW STUDY from the University of California offers a series of recommendations for financing increased use of PrEP, even in the face of current public policy financial constraints that are confronting both states and the Federal Government.

Conducted for Project Inform, a San Francisco, CA-based HIV advocacy organization, the report points out that several clinical and cost-effectiveness studies demonstrate that PrEP has the potential to reduce HIV infection rates for high-risk men who have sex with men (MSM) in a cost-effective way.

However, the study notes, policymakers must contend with the “current political reality of constrained financial resources for public health assistance, including for state Medicaid programs and for HIV prevention programs that serve individuals at high-risk of HIV infection.”

The study cited the multi-national iPrEX study financed by the National Institutes of Health (NIH) and the Bill and Melinda Gates Foundation, which demonstrated that a daily oral dose of the combination antiretroviral medication FTC-TDF, marketed as Truvada by Gilead Sciences, when administered with follow-up HIV testing, safety screening, risk reduction counseling, and condom distribution, can reduce the rate of HIV infection among high-risk MSM and transgender women.

Among all iPrEX study participants, those who received PrEP had a 44 percent reduction in HIV acquisition. Study participants with at least 90 percent adherence experienced a 73 percent reduction in HIV acquisition compared to participants who received a placebo pill.

The report noted that in January 2011, the Centers for Disease Control and Prevention (CDC) released interim guidance that offers conditional support for providers to prescribe FTC-TDF “off-label” as PrEP to high-risk MSM. In addition, the author said conversations and meetings with major private insurers reveal a willingness to reimburse PrEP in the limited circumstances described by the CDC’s guidance.

The report said Gilead Sciences has indicated a willingness to consider a Patient Assistance Program (PAP) to provide PrEP to certain low-income individuals, and that many state Medicaid programs appear willing to reimburse PrEP.

The study offered these recommendations to assist with PrEP financing:

- Support Gilead’s request for FDA approval of a prevention label for Truvada.
- Encourage the NIH and CDC to finance demonstration projects.
- Ensure public health insurance coverage for PrEP through state Medicaid programs.
- Ensure private health insurance coverage for PrEP.
- Advocate that Gilead develop a Patient Assistance Program for PrEP.
- Encourage non-Truvada PrEP formulations and promote price breaks for Truvada.
- Promote PrEP in tandem with other combination approaches to HIV prevention.
HIV Specialist Exclusive

Stopping the Spread

CDC’s Dr. John Brooks discusses new guidelines for clinicians currently being finalized

The Centers for Disease Control and Prevention (CDC) is updating its guidelines under its Prevention IS Care—Act Against AIDS campaign for HIV prevention, aimed at helping providers encourage their patients to avoid risky behaviors that could spread the virus to others.

HIV Specialist interviewed John T. Brooks, MD, an HIV clinician and medical epidemiologist at CDC, regarding these latest recommendations that he has helped develop. In addition to his work at CDC, Dr. Brooks also sees patients weekly at the Veterans Administration Hospital in Atlanta, GA, which operates the largest HIV clinic within the VA system.

Can you discuss briefly the importance of prevention with patients already living with HIV?
Prevention with patients with HIV infection is a critical component of comprehensive care. When you see patients, you are first concerned about their health, but you also need to be concerned about helping them reduce their risk of transmitting HIV to others.

When I meet with a patient, my first consideration is what I am doing for that individual. But I also need to be concerned about what I can do to help the patient, if needed, reduce their sexual risk-taking behavior, which helps protect them from sexually transmitted diseases (STDs) while also helping them reduce their risk of transmitting to others.

By encouraging patients to take their medications, they get maximum benefit of treatment and their HIV viral load is reduced, which has been shown to very substantially reduce their risk of passing on the disease to sex partners.

So it is important for those of us who treat patients to consider treatment as an important form of prevention.

What role can the HIV care provider, the person who treats these patients, play in helping to prevent spread of the disease?
One of the unique aspects of HIV care is that clinicians have the opportunity to interact with patients on a frequent basis, usually every three to four months. This can certainly be stretched out when patients become stable and the virus is under control. But every time you see a patient you have an opportunity to help him or her with prevention messages.

Once a patient is in routine care, a very simple intervention is to ask them “What are you doing sexually? What about drug and alcohol use? How are you doing about taking your medication?” Addressing these issues helps the patient and also helps them reduce the risk of transmitting to others.

I’ve encountered clinicians who were hesitant to talk to patients frankly in this way because they were afraid that they might be

blameful or that it might get in the way of their relationship with the patient. But engaging the patient in efforts to reduce their risk of transmitting HIV to others can be empowering for many patients if they are in the right mindset. It allows them to do something to help end this epidemic by protecting their partners.

Clearly, you must know the person you are working with, and you must make a careful judgment, but at the right moment, if the patient is open, you can engage them.

A good example is routine screening for STDs. We do this first to make sure the patient does not have an STD because over 90 percent of patients with an STD have no symptoms. The patient may not know that they have a problem. You can identify and treat the STD and that will benefit their overall care. It also reduces his or her risk of passing that STD to somebody else. And whether they have an STD or not, STD testing offers an opening to a conversation to discuss need to minimize risky behavior. If the patient has contracted gonorrhea, it’s likely he or she was engaging in risky behavior. So the diagnosis of STD is an opportunity to discuss those behaviors and to say, “Let me help you make it better.”

If a patient says, “Doc, I’ve been drinking and using meth and I don’t remember what happened, I just let my defenses down and didn’t use protection like I should have;” it is a great opportunity to help the patient address issues they may be having with drug abuse or alcohol addiction; addressing these issues can help them prevent passing HIV on as well.

What are some of the new Prevention IS Care recommendations that will be included in the updated guidelines?
In the current guidelines, the important message is that we put the patient first. Our recommendations are designed to prevent transmission, but the patient’s own disease is always the first concern. The new recommendations are in a number of areas, including, making sure that when the patient is diagnosed, he or she is linked to care and that they come in for regular medical visits. Unfortunately, a substantial percentage of patients diagnosed with HIV infection still are not effectively linked to care. By increasing the number of patients who are linked to care, we increase the number of patients who can be treated to reduce their HIV viral load. Getting linked to care is also an opportunity to assess risk behavior and mental health and make sure they are getting ap-
propriate care, if indicated, even if their HIV is not going to be treated right away.

Adherence to care and adherence to taking medication as prescribed is another important area of these recommendations. Taking a pill every day and remembering to do it is hard for some people. We are talking about a medicine you must take for the rest of your life. If you take it as prescribed, it reduces the HIV viral load substantially and reduces the risk of transmitting to others.

There is also a set of recommendations around routine STD testing and partner services; this area is a critical component, as well. We want to help clinicians think proactively and help them engage partners of the patient so these persons can be tested for STDs and HIV.

**What is your view of the recent studies that indicate that drugs used to treat AIDS can be used effectively for prevention?**

We have had some remarkable new data emerge in the last year; it’s some of the best news for HIV prevention that we’ve had in many years. Studies have now confirmed that treating patients relatively early in the course of their HIV disease substantially reduces their risk of transmitting to others.

Sometimes we are asked why we aren’t already treating more people. In 1996 when triple therapy became available, we began to use it widely, but it came at a cost. It was a lot of medication with substantial side effects, so we were often weighing the value to the patient in accepting all of these side effects against treating their HIV. At that time, many clinicians waited as long as possible before prescribing these drugs so as to limit these side effects and the difficulty of taking a large number of pills for the rest of the patient’s life.

A number of modeling studies suggested that by treating large populations (in other words, most people with HIV infection regardless of their stage of disease) we could reduce the epidemic, but it was not a viable option at that time because the medication was so difficult to take. However, over the last few years, tremendous advances have been made. The drugs are more potent, have fewer side effects and are simpler to take. Many patients now can take only one pill once a day and experience minimal side effects.

More recent population-based epidemiologic studies have suggested that treatment was leading to a decline in new infection, and other studies provided biomedical evidence that if you suppressed the amount of virus in plasma it reduces the amount of virus in genital secretions and, therefore, likely reduces the risk of passing on the virus. This year’s landmark HIV Prevention Trials Network (HPTN) 052 study addressed this question with a randomized controlled trial and demonstrated very persuasively that treatment reduced transmission of HIV infection to the patients’ uninfected partners by 96 percent. That was truly remarkable and what we had hoped for.

But the study also showed that taking medication was not enough—it is important to remember that patients in this study, just like other persons living with HIV infection, needed to receive recommended counseling and take other precautions to minimize transmission to others. These included counseling on safe sex practices, free condoms, treatment for STDs, and treatment for any complications related to living with treated HIV infection such as drug side effects that might make it hard for a patient to adhere to therapy.

That study included heterosexual couples. Do you believe the results would also apply to men who have sex with men (MSM)?

I believe there is biological plausibility that the results of this study can be translated to MSM. It is hard to estimate what the differences in efficacy would be for MSM compared with heterosexuals. We treat MSM with HIV infection first because they have the infection, and it is plausible to say to a patient that when he is being treated, the treatment very likely will reduce his risk of transmitting HIV, but that he needs to use condoms and take all other available steps to maximally reduce his risk of transmitting—and that these same steps help protect him from getting an STD.

We also don’t have any data from IV drug users, but once again, we are going to prescribe ART because it is needed for that patient’s health with the added benefit that there is good evidence that treating the infection will very likely reduce that person’s risk of transmitting HIV to other persons.

There is one exception. There are occasionally patients who have high CD4 cell counts and who may not need treatment yet, but who regularly engage in high risk behavior despite counseling or come in repeatedly with an STD. We may discuss with that person the advisability of taking ART specifically to reduce their risk of transmitting HIV to others.

**What action, if any, should the federal government take to support this effort?**

Our responsibility at CDC is to put scientific evidence in to the hands of decision-makers so they can use it. We have evidence that treatment can be a very potent form of prevention. We can arm those who can make the decisions about funding with that information.

This epidemic is enormous and is not going away; today an estimated 1.2 million Americans are infected and a little less than half of them are unaware of their infection. We need to do everything possible to get these people into care. Treatment is not only good for the individual patient; it is good for the public health. We need to add every weapon possible to our toolkit to bring this epidemic to an end.

**What is the status of the guidelines now?**

Publication of the new guidelines is expected sometime in 2012. They are in draft form now and are being vetted by stakeholders, including the American Academy of HIV Medicine, state health departments, clinicians and other agencies.

**How can providers learn more about the Prevention IS Care campaign?**

The whole purpose of Prevention IS Care is to arm the healthcare provider with tools to help provide effective care to patients with HIV. A new Prevention IS Care Resource Kit with updated tools for HIV providers and patient education materials will be available from CDC in October. It is part of CDC’s overall Act Against AIDS program. For more information on Prevention IS Care or to order the new resource kit in October, visit [http://www.actagainstaids.org/provider/index.html](http://www.actagainstaids.org/provider/index.html).
UNC Receives Second NIH Grant

Days after receiving a $32 million grant to lead AIDS research in collaboration with eight universities, UNC scientists received a $3 million grant from the National Institute of Allergy and Infectious Diseases (NIAID) to develop and test new treatments aimed at preventing sexual transmission of HIV to uninfected individuals.

The NIAID award is titled Next Generation Pre-Exposure Prophylaxis, or PrEP. “We need to be ahead of the virus and to start working on HIV therapies that will be available for the next generation, which is the aim of this NIH initiative,” said J. Victor Garcia-Martinez, PhD, the project’s principal investigator and professor medicine, and a member of UNC’s Center for Infectious Diseases and Center for AIDS Research.

Project collaborators with Garcia-Martinez are Angela Kashuba, PharmD, associate professor, and Russell Mumper, PhD, McNeil Distinguished Professor, both in the UNC Eshelman School of Pharmacy, and Daria Hazuda, PhD, at Merck Research Laboratories. Merck will not receive federal funding from this award. “We will address issues of fundamental importance to the next generation of PrEP agents,” Garcia-Martinez said.

The new project will explore candidate drugs, experimental compounds, not yet tested in people. Preclinical experiments will be conducted in humanized BLT mice that were created by introducing human bone marrow, liver and thymus tissues into animals without an immune system of their own. Humanized BLT mice have a fully functioning human immune system and can be infected with HIV in the same manner as humans. The laboratory of Garcia-Martinez has pioneered the development of this humanized mouse model.
Objective 1: Identify molecular mechanisms underlying proviral latency and HIV persistence despite antiretroviral therapy;
Objective 2: Discover drug candidates and therapeutic approaches capable of depleting persistent infection;
Objective 3: Establish informative animal model systems to study HIV persistence and test therapeutic strategies;
Objective 4: Study the basis for viral persistence in humans, and develop new approaches to the testing of I/E therapy.

Collaborative Team
To accomplish these ambitious objectives, we have assembled a team of 20 leading experts who have collectively pioneered and led the study of HIV latency over the last 15 years.

Collaboratory universities, along with UNC, are Case Western Reserve University; Johns Hopkins University; University of California, Davis; University of California, Los Angeles; University of California, San Diego; University of California, San Francisco; The Gladstone Institute; University of Minnesota; and the University of Utah.

Because lifelong ART presents formidable problems, among the many important goals for future HIV research is the development of temporally contained therapies capable of eradicating HIV infection. We have demonstrated that VOR or suberoylanilide hydroxamic acid, a potent drug licensed for use in oncology, is a selective inhibitor for Class I histone deacetylases (HDACs), key enzymes that enforce latency of HIV. VOR is able to induce latent HIV expression in cell lines, and virus production in the laboratory from the resting CD4+ T cells of antiretroviral-treated, aviremic HIV-infected patients.

Here at UNC, we are also conducting a clinical experiment in HIV patients with the drug VOR, one of the first such studies in the world. This clinical study compares HIV RNA expression within resting CD4+ cells in HIV-infected patients on stable ART before and after VOR dosing; and will characterize the safety, tolerability and spectrum of side effects of VOR in adult patients with HIV-1 infection receiving combination antiretroviral therapy. In short, this project may validate the ability of HDAC inhibitors to contribute to the purging of persistent infection, and establish a new paradigm for early phase human testing of such approaches.

The progress made so far in gaining a detailed understanding of HIV biology and pathogenesis, and the stunning achievements of ART should give us hope that we can overcome the recognized and the yet-to-be-discovered challenges of persistent HIV infection.

ABOUT THE AUTHOR: David Margolis, MD, is a professor of medicine, microbiology and immunology, and epidemiology at the University of North Carolina at Chapel Hill. Dr. Margolis’s laboratory studies interactions between HIV and the host cell to improve the treatment of HIV infection and attack, and perhaps eradicate, persistent HIV infection.
The AIDS Research Institute (ARI) coordinates and integrates all HIV/AIDS research activities at the University of California, San Francisco (UCSF). The ARI stimulates innovation and supports interdisciplinary collaboration aimed at all aspects of the epidemic domestically and around the world.

The ARI brings together hundreds of scientists and more than 50 programs from throughout the university and affiliated labs and institutions around the world to foster innovative and integrated science, including basic, clinical, prevention, and policy research, to prevent, understand, treat, and someday cure HIV infection. Currently, ARI researchers are leading or participating in dozens of open clinical and prevention trials at sites all over the world.

Since the disease was first reported 30 years ago, UCSF has been fighting this global scourge. We’ve made incredible advances—from the development of new drugs and promising vaccine candidates to breakthroughs in clinical research and care to establishing groundbreaking prevention and education programs in dozens of countries.

In just the last year, we have learned that biomedical prevention tools like microbicides and the use of antiretrovirals before infection among individuals at high risk of HIV infections can be effective in slowing the spread of this disease. The findings of the iPrEx study, led by investigators from the ARI affiliated Gladstone Institute for Virology and Immunology, showed that HIV-uninfected men who have sex with men at high risk for HIV infection taking a once daily single pill containing two antiretrovirals were able to greatly reduce their chances of becoming infected.

This finding was confirmed with similar results in a parallel study in Sub-Saharan Africa where the preventive effect of daily antiretroviral dosing by high risk uninfected individuals was tested in heterosexual couples in which one partner was infected with HIV and the other was HIV negative.

Our researchers are on the cutting edge of an evolving understanding of how HIV damages systems throughout the body in previously unseen ways, contributing to the premature aging of those living with HIV. Based on this knowledge of how HIV begins to damage major organ systems in patients from the moment of infection, our Positive Health Program at San Francisco General Hospital became the first clinical program in the country to recommend to patients that they start antiretroviral treatments upon diagnosis of HIV infection. This policy has been adopted citywide by the ARI affiliated San Francisco Department of Public Health.

In addition, the recommendation to offer treatment upon diagnosis could lead to additional population wide prevention benefit. A recent study, conducted in part at a UCSF affiliated site in Africa and again looking at heterosexual couples where one partner is infected and the other is uninfected, found that treating the infected person with antiretrovirals reduced their partner's chances of becoming infected with HIV by 96 percent.

UCSF researchers led a multi-center study that demonstrated that HIV-infected kidney transplant recipients can have as good an outcome as non-infected individuals. In addition, the immunosuppressive drugs they take post-transplant do not increase their risk of complications from HIV infection.

Perhaps most exciting of all, our scientists are leaders in international efforts to understand HIV latency among those who are infected and work toward its eradication—effectively, a cure. The “Berlin Patient”, the first person cured of HIV, is being seen at UCSF and ARI affiliated researchers have recently received significant funding from the National Institutes of Health to develop strategies to eliminate HIV from a patient’s body.

We participated in drafting the first-ever National HIV/AIDS Strategy and advocate for its effective implementation. ARI investigators are taking part in the Department of Health and Human Services 12 cities project, which seeks to implement and test a comprehensive HIV prevention, testing and treatment program in a dozen American cities with the highest HIV burden with a goal to develop integrated interventions that dramatically change the course of the HIV epidemic in the United States.

At the AIDS Research Institute, our goal is a world without AIDS. The accelerating innovation observed in just the last few years suggests this dream is, after 30 long and difficult years, imaginable.

**ABOUT THE AUTHOR:** Dr. Greenspan, BDS, PhD is professor of oral pathology and pathology in the UCSF Schools of Dentistry and Medicine, serves as the associate dean for global oral health and has served as ARI director since 2003.
Roche Molecular Diagnostics: Technologies Advancing HIV Medicine

BY TRI DO, MD, MPH

Viral Load Testing

Viral load testing is a cornerstone of HIV treatment management and a surrogate marker for antiretroviral drug approval. Table 1 shows a timeline of RMD's viral load development. Because HIV mutates quickly, the COBAS® AmpliPrep / COBAS® TaqMan HIV-1 Test, version 2 (TaqMan v2.0) targets both the gag and LTR region and has the highest sensitivity of any commercial test to date.

With the introduction of more sensitive real time PCR, some patients previously suppressed (<50 copies/mL) using the older endpoint PCR assays have developed intermittent low-level viremia (LLV) of 50-200 copies/mL. Available evidence suggests that this LLV is real, does not indicate emerging drug resistance nor require a regimen change, and is not due to assay artifact or laboratory error as reflected in the most recent US treatment guidelines (Table 2).

Future Directions

HIV Morbidity and LLV—The clinical significance of higher sensitivity testing is currently under study. Ongoing viral replication and associated systemic inflammation may be linked with development of premature cardiovascular, kidney and liver disease. RMD is collaborating with several cohort studies in assessing the relationship between residual viremia, inflammatory markers and HIV morbidity in the HAART era.

HIV Eradication—Evidence indicates that viral decay occurs in two major compartments: one with two phases of rapid decay over four weeks, and a second with a slower rate of decay, with residual, very low level viremia persisting for years. This second compartment may represent virus from latent reservoirs, the HIV eradication target, measurable with the SCA. RMD is supporting eradication research with modifications to its commercial assay to provide single copy sensitivity.

Deep Sequencing Resistance Testing—Low-frequency HIV-1 resistance mutations, especially NNRTI mutations, are associated with an increased risk of virologic failure with first-line regimens. Current resistance assays detect minor variants as low as 20 percent of total virus population. Ultra-deep Sequencing (UDS) detects previously undetected, low abundance mixtures (1-3 percent of species).

RMD is collaborating in cohort studies evaluating the 454 Life Sciences UDS drug resistance genotyping assay for optimal regimen selection in treatment-naïve and experienced patients.

The AmpliCare Program—ART scale-up programs in developing countries have seen significant rises in drug resistance due to the lack of viral load monitoring as presented at CROI 2011 (e.g., abstract numbers 53, 109, 623). Roche's AmpliCare program offers low-cost, sustainable VL assay pricing to the World Bank's least developed and low-income countries.

Roche Molecular Diagnostics are committed to reducing HIV morbidity, ensuring equal access to quality HIV care, and supporting efforts to ending the HIV epidemic.

Table 1. Advances in VL Technologies

<table>
<thead>
<tr>
<th>Assay (Year of FDA Approval)</th>
<th>Endpoint PCR</th>
<th>Real time PCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMPLICOR® v1.0 (1995)</td>
<td>400–750,000</td>
<td>48–10,000,000</td>
</tr>
<tr>
<td>COBAS® AMPLICOR® v1.5 (1998)</td>
<td>50–750,000</td>
<td>20–10,000,000</td>
</tr>
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Table 2. US Treatment Guidelines: Key Medical Decision Points

- Optimal viral suppression: VL persistently below the level of detection (LOD; <20–75 copies/mL, depending on the assay).
- Virologic failure: confirmed VL >200 copies/mL, eliminates viremia caused by “blips” or assay variability based on AIDS Clinical Trials Group data.
- “Blips: transiently detectable VL <400 copies/mL; not uncommon in successfully-treated patients.
- Low level positive VL (<200 copies/mL): may be more common with some assays; no definitive evidence demonstrates increased risk for virologic failure.
- Managing LLV: assess treatment adherence; monitor VL trends over time. No specific monitoring schedule is suggested.

References

5 Li et al. JAMA 2011;305:1327-55.

ABOUT THE AUTHOR: Tri Do, MD, MPH is Director: Clinical Research & Scientific Affairs at Roche Molecular Diagnostics, Pleasanton, CA
Merck and Collaborators Forge Ahead with Studies to Eradicate HIV

By Daria J. Hazuda, PhD and Michael J. Harbour, MD, AAHIVS

Since the introduction of highly active antiretroviral treatment (HAART) for the treatment of HIV infection, the morbidity and mortality of the disease has dramatically declined, and the life expectancy for those living with HIV and AIDS has significantly improved.

Despite these tremendous advances, the prospect of lifelong therapy presents many challenges. In addition, the epidemic continues in both the developed and developing world, and the prospect for a vaccine to prevent infection has remained elusive. The recent attention on the American citizen living in Berlin (the “Berlin” patient) who experienced a “cure” from HIV due to a bone marrow transplant for treatment of an unrelated leukemia has intensified the efforts to develop new therapies to achieve such a cure.

Two different types of approaches to HIV cure have been postulated. The first is a “functional” cure whereby the body is able to control ongoing viral replication without the use of antiviral medications in a method similar to elite controllers. Genetic advantages and innate immunity play a role in the ability of some patients to better control the virus.

The second approach is a “sterilizing cure” whereby the virus is eradicated from the body and no further antiviral treatment is necessary. A bone marrow transplant is not an ideal approach due to its associated toxicity and morbidity, but other potential approaches are currently being investigated.

These interventions are routed in a growing understanding of the reasons that HIV cannot be cured using currently available antiretroviral drugs. These include long-lived latently HIV-infected cells and residual HIV viral replication in addition to viral reservoirs which are difficult to penetrate. An anergic immune system coupled with a state of ongoing inflammation results in the replenishment of this dynamic reservoir and persistent viremia. These ideas are not mutually exclusive, and ultimately combining interventions which address several of these mechanisms may be required.

On July 11, 2011 Merck announced that company researchers will collaborate with the teams led by the prominent academic Institutions University of North Carolina ( UNC) and University of California at San Francisco ( UCSF) to develop new approaches to eradicate HIV.

The UNC team and Merck will begin to study HIV latency and identify ways to purge persistent HIV viral infection from the body. The UCSF team along with an international team of academic, governmental and Merck scientists will work to define and understand the body’s HIV reservoir and potential treatments. The NIH is the primary funding organization for both studies and Merck will not receive any payment for its collaboration.

Merck is one of the few pharmaceutical companies that has been involved in multiple stages of HIV research including studies for preventive vaccines, treatments, and now eradication. There are numerous challenges to conducting curative research studies. Robust assays and biomarkers to assess overall latent viral burden still need to be developed. In addition, animal models for testing need to be developed and tested for efficacy. And finally clinical trials and treatment guidelines need to be developed by working with the medical and patient communities.

Merck remains committed to the field of HIV/AIDS and continues to pursue multiple avenues for treatment of patients throughout the world.
Gilead Pipeline Update: A Focus on Single Tablet Regimens

**BY DANIELLE POULIN PORTER, PHD AND TODD FRALICH, MD**

GILEAD SCIENCES has an ongoing commitment to advancing therapeutics and improving patients’ lives through the development of single tablet regimens (STRs) for the treatment of HIV/AIDS.

Gilead recognizes the clinical benefits to patients of simplified treatment regimens. STRs combine a complete highly active antiretroviral therapy (HAART) regimen into a single pill that is dosed once daily. Gilead believes that the development of additional STRs will provide further treatment options for patients seeking regimen simplification.

The newest STR, Complera (FTC/RPV/TDF), which was approved by the Food and Drug Administration (FDA) August 10, 2011, consists of a combination of emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) and rilpivirine (RPV), a non-nucleoside reverse transcriptase inhibitor (NNRTI).

In the subset analysis of the pooled phase 3 clinical trials ECHO and THRIVE, RPV demonstrated non-inferior efficacy and improved tolerability compared to efavirenz (EFV) through 48 weeks (HIV-1 RNA <50 copies/mL 84% vs. 82% in the FTC/TDF + RPV and FTC/TDF + EFV arms, respectively; ITT-TLOVR).1 Three additional phase 3b studies are currently ongoing to assess the safety and efficacy of FTC/RPV/TDF in treatment naïve patients, as well as evaluate the safety and efficacy of switching from either a boosted protease inhibitor (PI/r)- or NNRTI-based regimen to the FTC/RPV/TDF STR in virologically-suppressed patients.

The next STR is the Quad, which is anticipated in 2012 and will be the first integrase strand transfer inhibitor (INSTI)-based STR. The Quad will contain two novel agents, the HIV integrase inhibitor elvitegravir (EVG) and the pharmacokinetic enhancer cobicistat (COBI), in combination with FTC/TDF.

The Quad displayed unsurpassed efficacy in phase 2 through 48 weeks (HIV-1 RNA <50 copies/mL 90% for the EVG/COBI/FTC/TDF arm) and recent results from the first phase 3 comparative integrase inhibitor study showed that once daily EVG was non-inferior to twice daily raltegravir in treatment experienced patients.2,3 Two additional phase 3 studies in treatment naïve patients are currently ongoing to investigate the safety and efficacy of the Quad STR compared to an NNRTI- or atazanavir-based regimen.

Investigational agents currently in development may provide further opportunities for the formulation of future STRs, including a planned PI-based STR combining GS-7340, FTC, COBI, and darunavir. Currently in phase 1b, GS-7340 is a novel amidate tenofovir prodrug that has the potential to improve upon the safety and efficacy of TDF by targeting delivery of high concentrations of tenofovir to lymphoid cells.4 This increased specificity and potency should allow for a lower dose of GS-7340 relative to TDF and permit the development of new STRs that are not possible today.

Gilead is dedicated to providing access to safe, effective, and convenient therapeutic options to patients regardless of where they live. Gilead’s network of distributors and licensing agreements with multiple international manufacturers ensure that high-quality versions of Gilead’s HIV medications are affordable and available to patients in the developing world.

Because of the demonstrated advantages of STR therapies in the management of HIV, Gilead will also seek to develop future STRs for the treatment of other chronic diseases such as hepatitis C virus infection. Applying the knowledge and experience gained in the development of optimal HIV treatments will hopefully advance the care of patients suffering from life-threatening diseases across therapeutic areas and around the world.

**The newest STR, Complera (FTC/RPV/TDF) was approved by the Food and Drug Administration August 10, 2011.**

**ABOUT THE AUTHOR: Danielle Poulin Porter, Ph.D., is Medical Project Manager, HIV Medical Affairs, at Gilead. She received a Ph.D. in Virology from Harvard University and has research experience in HIV, HCV, and oncology. Dr. Porter previously worked on biodefense policy and national security issues.**

**ABOUT THE AUTHOR: Todd Fralich, M.D., Director, HIV Medical Affairs at Gilead, manages medical information and clinical trials for Truvada, Atripla and recently the Single Tablet Regimen, Complera. Dr. Fralich joined Gilead after many years as an HIV physician in South Florida. He completed medical school at Rush Medical College and internal medicine residency at Northwestern University.**

See References on page 37
ABBOTT has a long history in the fight against hepatitis and HIV that began 40 years ago when the first hepatitis diagnostic assay was introduced in the early 1970s followed by the first HIV diagnostic assay in the mid-1980s.

The Abbott RealTime viral load tests run on the Abbott m2000 system that uses real-time polymerase chain reaction (PCR) to amplify, detect, and quantify HIV and hepatitis viral nucleic acids from patient blood samples. The Abbott m2000 system automates the important steps of the process, from sample preparation to data analysis, allowing laboratories to process molecular tests efficiently, accurately and confidently.

The growing prevalence of HIV-1 non-B subtypes and circulating recombinant strains in the US has made accurate viral load detection more complex. The Abbott RealTime HIV-1 assay for detecting variant subtypes has been well established in the literature and allows physicians to confidently monitor viral load levels and optimize anti-retroviral drug treatment. The Abbott RealTime HIV-1 assay is one of the fastest and most sensitive viral load tests available and has the ability to detect and precisely measure group M, N and O strains of HIV-1, as well as all known non-B subtypes.

In addition to HIV-1 viral load testing Abbott Molecular also offers FDA approved tests for the measurement of hepatitis B (HBV) and hepatitis C (HCV) viral loads from blood samples. The RealTime HCV viral load test has a limit of detection (LOD) and limit of quantification (LOQ) of 12 IU/L, which distinguishes this assay from other commercially available HCV viral load assays.

Abbott’s Retrovirus Assay Milestones

Abbott’s Global Pharmaceutical Research and Development division antiviral program is focused on finding new treatment options for HCV, which affects more than 180 million people worldwide, with approximately 3 to 4 million people newly infected each year. Abbott is one of just a few companies with several drug classes in development that block HCV replication and prevent the virus from attaching to other cells. The goal is to shorten the duration of treatment, improve tolerability over current therapies, and increase cure rates.

Abbott Molecular has an ongoing commitment to clinical research in the area of HIV and hepatitis diagnostics. It is an important goal for the scientific affairs team to help physicians and patients to understand the clinical utility and importance of the diagnostic assays that Abbott has to offer.

For more information on our US and Global Scientific affairs activities or research collaborations, contact can be made through Gavin Cloherty, PhD (gavin.cloherty@abbott.com) or Tom Young, NP, MS, PhD, AAHIVS (tom.young@abbott.com).

ABOUT THE AUTHOR: Gavin Cloherty, PhD, a molecular biologist, has been with Abbott Molecular for 10 years and was involved in the initial research and development of the m2000 system and HIV viral load studies. He specializes in laboratory technology mechanics and genetics and is an Associate Director for Scientific Affairs with Abbott Molecular’s global program in infectious disease (HIV, hepatitis, TB, and CT/NG).
Prevention of Transmission to the Sero-Negative Partner
An overlooked, but growing, indication for antiviral therapy

There has been a great deal of discussion over the past two years about when to start antiviral therapy – with the focus mainly on the patient’s CD4+ count. The current acceptable U.S. standard starting ART is now with a CD4 count of < 500 cells/mm3.

Other perhaps lesser known indications include chronic Hepatitis B infection or HIV-associated kidney disease. Another indication not frequently discussed but noted in the most recent IAS-USA guidelines “Risk for secondary HIV transmission is high, e.g., serodiscordant couples”.

Although cited as only level B II evidence I believe that when both the IAS and DHHS guidelines are updated serodiscordance will receive greater emphasis as a treatment indication.

I would argue that from a practical as well as a scientific perspective this has always been at least a very reasonable thing to do. There also is now growing published data (not yet incorporated into most recent HIV treatment guidelines) that lend support to this practice.

Looking back at the history of the clinical scenario of serodiscordance, there is actually data from Quinn et al that was published in 2000 where he found a direct correlation between viral load and sexual transmission among their cohort of serodiscordant couples (n=415) in Uganda who they followed for up to 30 months. Quinn found no cases of HIV transmission if the viral load was < 1500 copies/ml.2 We also know from many prenatal studies that maternal viral load is the key determinant of transmission, which rarely occurs if the HIV-RNA level is < 1000 copies/ml.

A more recent meta-analysis by Attia and colleagues looked at 11 different cohorts involving 5,021 heterosexual couples. They found no HIV transmission in persons with a viral load < 400 copies/ml while taking ART.3

A systematic review from the Cochrane database that included seven observational studies found that in patients who had a CD4+ count of > 350 and on ART there were 0 (zero) HIV transmissions and 61 infections among untreated couples.4

In perhaps the most compelling study to date, an NIH sponsored trial (HPTN 052) that took place in Asia, Africa, and the Americas of 1,763 serodiscordant couples (97 percent heterosexual) and CD4+ counts of 350-550 cells/mm3 randomized half to start ART and the other half to wait until the CD4 count dropped below 250. In 28 cases of genetically confirmed new HIV infection from the same partner, 27 cases occurred in the delayed ART group. This represents a remarkable 96 percent reduction in transmission risk.

The authors believe that sustained suppression of HIV-1 in genital secretions is the most likely mechanism of HIV prevention.

My own clinical practice for the past several years has been to encourage therapy for all discordant couples, although this is not all data from Quinn et al that was published in 2000 where he found a direct correlation between viral load and sexual transmission among their cohort of serodiscordant couples (n=415) in Uganda who they followed for up to 30 months. Quinn found no cases of HIV transmission if the viral load was < 1500 copies/ml.2 We also know from many prenatal studies that maternal viral load is the key determinant of transmission, which rarely occurs if the HIV-RNA level is < 1000 copies/ml.

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See Best Practices on page 32
HIV Providers Score Testing Policy Win in Pennsylvania

The 2006 Morbidity and Mortality Weekly Report (MMWR) issued by the Centers for Disease Control and Prevention (CDC) that recommended routine HIV screening for all Americans was the starting point for a series of policy changes across the United States over the last five years. AAHIVM was one of the early endorsing organizations of the new recommendations, and worked with CDC and other organizations to inform changes to state laws and codes that would support the practical implementation of the new recommendations.

Many state laws on HIV testing protocols and confidentiality were drawn up prior to the Health Insurance Portability and Accountability Act (HIPAA) and the Americans with Disabilities Act (ADA) that created discrimination and privacy protections for persons newly tested for or diagnosed with HIV. While these state laws guarded against unfair practices in the workplace and detrimental disclosure of health information, they also complicated the movement in those states towards routinely screening residents for HIV.

For example, CDC recommended removal of previously-codified requirements for separate written consent for a test that, early in the history of the disease, patient advocacy groups had insisted were necessary to prevent patients from receiving a test that might result in personal stigma or even discrimination against them personally.

By 2006 the medical confidentiality and discrimination laws, along with insurance codes in many states, had addressed many of these concerns and the focus shifted to the public health battle of identifying new infections. The CDC determined that presenting patients with pages of legalese about the HIV test and requiring a separate signature over and above the required general consent for care created a barrier to patients accepting the test. There was a strong push in most states to legislatively eliminate barriers to the goal of testing everyone between the ages of 13 and 64 for HIV infection.

The Pennsylvania Story
Going into 2011, Pennsylvania was one of only five states remaining that had not successfully removed its legislated barriers to implementing the CDC recommendations. The Pennsylvania Chapter of AAHIVM has long been one of the Academy’s most active in terms of political advocacy on HIV provision-of-care issues. Several Chapter Steering Committee members had served on a stakeholder workgroup convened by the state health department in 2007 to consider changing Pennsylvania’s Act 148 that addressed HIV testing provisions. The Act, originally drawn up in 1990, included provisions that make it cumbersome to routinely test for HIV: mandated separate written consent, required pre-test counseling for everyone taking a test, and requisite in-person follow-up visits for post-test counseling and test results (including those who tested negative for HIV infection).

The Pennsylvania State Department of Health, the regional AETC, the stakeholders’ workgroup (including participating AAHIVM Members), the Pennsylvania Medical Society and many other groups and individuals in Pennsylvania all recommended and endorsed substantial legislative changes to Act 148 to address these points. Specifically, the Department of Health, the Academy and others recommended changing the requirement for separate written consent as stipulated in the original law to “documented consent.” This change would allow hospital emergency departments and other providers to quickly secure and record consent for a test from the patient without requiring a signature separate from the general consent required for treatment.
Also recommended was a removal of the codified requirement for elaborate pre-test counseling for every individual taking a test. Counseling and elaboration on HIV disease, its risk factors, transmission, diagnosis and treatment, could be done at the provider’s discretion based on individual cases, or through provision of written materials. This is not to be confused with outright ending of all prevention counseling or counseling referrals for at-risk individuals. Instead, it allows providers to determine how best to communicate information to their patients in a format that is readily understood and appropriate for the patient.

Lastly, it was widely agreed that the state’s requirement to have every tested individual return in person for a second visit to receive results and additional counseling on what test results mean and on prevention issues was hindering testing of all patients at least once as the CDC suggests. In Pennsylvania, that requirement applied even if the test result is negative for HIV infection—a strong hindrance to delivering results in a quick, effective way and something not required in terms of testing for any other disease.

Following the lead of the Pennsylvania Department of Health and the recommendations of the 2007 workgroup, some state lawmakers began working to change the existing law accordingly. AAHIVM Members in the state contacted lawmakers via emails, phone calls and in-person visits to put Pennsylvania HIV testing policy in line with most of the rest of the country. One state senator in particular, Sen. Ted Erickson, had introduced a bill in every legislative cycle beginning in 2007 (following the workgroup’s recommendations) that addressed the separate written consent and pre-test counseling barriers. Only in 2010 did his bill receive enough support to be sent to the Appropriations Committee, where it ultimately died.

The Road to Success
In 2011 it became clear that the political temperament in Harrisburg was finally such that Sen. Erickson’s perennial bill had a reasonably strong chance of finally becoming law. AAHIVM staff and provider members in Pennsylvania mounted a vigorous education and advocacy campaign in an effort to push the bill through both chambers and onto the governor’s desk. Visits were paid to the committees of jurisdiction in both houses of the Assembly, to leadership of both parties and to key administration and health officials in the state.

In May 2011, after several years of advocacy and education on the issue, AAHIVM Members and other groups were at last successful in moving the bill through the state Senate and into the House. When the House took up the Erickson bill, AAHIVM and the other supporters worked with the Department of Health to add an amendment to remove requirements for follow-up, in-person post-test counseling ONLY for patients with a negative test result. Throughout this process, some legal and civil rights groups threatened to hamper the common-sense efforts of testing advocates, but lawmakers were continually assured by the bill’s proponents that counseling would remain a key part of prevention, that patients would still be informed and given the chance to “opt-out” of testing, that consent would be documented and that patient anonymity and insurance coverage were well-protected by existing laws.

In June, the now-amended Senate Bill 260 sponsored by Sen. Erickson passed through the House and landed on Governor Corbett’s desk for signature. As a final and rewarding step in the process, AAHIVM providers and staff who had advocated for the bill were invited to participate in a ceremonial signing by the governor of the new Act 59 of 2011 on July 27.

Act 59 ensures that it will now be possible for more individuals to be tested for HIV in Pennsylvania, which ultimately should allow for better health outcomes for individuals who learn their status earlier and receive treatment, and should also allow for better public health outcomes in terms of a reduction in transmission from individuals who do not know their HIV status.

Interested in getting involved in your local chapter? Want to know more about pending HIV-related legislation in your state? Check out our Members-only online State Legislation Tracker at www.aahivm.org.
New Technology in Health Care Award to Recognize Innovation in HIV Care

The American Academy of HIV Medicine (AAHIVM) is pleased to announce a new award which recognizes the implementation of advanced technology into HIV care. AAHIVM has partnered with the Institute for Technology in Health Care (ITHC) to create the AAHIVM/Institute for Technology in Health Care HIV Practice Award, which will provide two $10,000 unrestricted cash rewards to a person(s) who has created, adapted and/or used innovative technology in their HIV practice and is willing to share that technology with others to improve patient care.

The use of technology in medicine has been growing over the last decade and will continue to do so. Advances will allow enhanced quality in patient care by improving communication between health care providers, between health care providers and patients, speeding the transmission of laboratory and radiologic data and in direct patient care by allowing remote examination and monitoring of patients. Potential applications in HIV care are extensive and growing. As an example, we discussed electronic medical records in previous issues of HIV Specialist and address electronic prescribing, or E-prescribing (eRx), in this issue.

Given these advances, in the Fall of 2010, the Institute for Technology in Health Care (ITHC), a small foundation located in Washington, DC, approached the Academy about partnering with them to help acknowledge and encourage innovative technologies in HIV care. It is a fitting partnership. ITHC is interested in stimulating innovative projects that use technology to benefit health and AAHIVM Members are front-line practitioners in HIV care.

The Academy accepted this challenge and established the AAHIVM/Institute for Technology in Health Care HIV Practice Award. ITHC generously contributed the two $10,000 unrestricted cash awards, to be administered by the Academy.

AAHIVM reached out to another partner, the Association for the Advancement of Medical Instrumentation (AAMI). AAMI is dedicated to increasing the understanding, safety, and efficacy of medical instrumentation. This organization has been collaborating for many years with the ITHC foundation offering a similar award to their members.

Early in 2011, the Academy established an awards committee of Academy physicians, physicians assistants, nurse practitioners, national board members and at least one non-AAHIVM member. I am pleased to chair that committee. Other members include: Marjorie Golden, MD, AAHIVS; Gary F. Spinner, PA, MPH, AAHIVS; Jim Scott, PharmD, AAHVIE; Kathryn Thiessen, NP, AAHIVS; and Ahmad Sajadi, MS (AAMI representative).

As a starting point, the committee agreed upon the following definition for medical technology: Medical technology encompasses a wide range of health care products which can be used to diagnose, monitor and treat disease. Such technologies are intended to improve the quality of healthcare delivered, and as a direct consequence, improve patient outcomes. Technology can positively impact education, communication, access to care, timeliness of diagnosis, treatment options, and length of stay.

Over the course of the last several months the awards committee has established the award criteria and an application process. To be considered for this award, a candidate must meet all the following eligibility criteria:

- Be a licensed health care provider in the United States.
- The practice can be defined as a private practice, a hospital or university based clinic, a group practice, a community health center, HMO, or other entity that provides direct clinical care to those with HIV disease.
- There must either be at least 200 HIV patients served by the practice or 50% of a smaller practice to be eligible.
- The technology used in the practice must be accessible to other HIV practices to improve their care of patients.
- Candidates must submit a completed application form describing the technology used in their practice to be considered for the award.
- Candidates for the award must be prepared, if they are selected, to publish a paper describing the technology in a professional journal in 2012.
- The selected candidate(s) will also present their innovative technology at a professional conference within 2012.
- All candidates for the award will be acknowledged on AAHIVM’s website, and will be featured with an article in the HIV Specialist magazine.
- Candidates may self nominate or be nominated by a colleague, with the permission of the candidate.
- AAHIVM’s Board of Directors and the members of the Technology Awards Committee are not eligible for the award.

Applications will be accepted through September 30th. The awards committee will serve as judges for deciding the recipients of the awards. The recipients will be recognized at the Academy’s Annual Friends and Members Reception in conjunction with the CROI conference in Seattle, Washington in March 2012. The application is available at the AAHIVM website, www.aahivm.org.
Post-marketing cases of liver injury, including some fatalities, have been reported. These have generally occurred in patients with advanced HIV-1 disease taking multiple concomitant medications, having co-morbidities including hepatitis B or C co-infection, and/or developing immune reconstitution syndrome. A causal relationship with PREZISTA/ritonavir therapy has not been established.

Appropriate laboratory testing should be conducted prior to initiating therapy with PREZISTA/ritonavir and patients should be monitored during treatment. Increased AST/ALT monitoring should be considered in patients with underlying chronic hepatitis, cirrhosis, or in patients who have pre-treatment elevations of transaminases, especially during the first several months of PREZISTA/ritonavir treatment.

Evidence of new or worsening liver dysfunction (including clinically significant elevation of liver enzymes and/or symptoms such as fatigue, anorexia, nausea, jaundice, dark urine, liver tenderness, hepatomegaly) in patients on PREZISTA/ritonavir should prompt consideration of interruption or discontinuation of treatment.

Severe Skin Reactions

During the clinical development program (n=3063), severe skin reactions, accompanied by fever and/or elevations of transaminases in some cases, have been reported in 0.4% of subjects. Stevens-Johnson Syndrome was rarely (<0.1%) reported during the clinical development program. During post-marketing experience toxic epidermal necrolysis has been reported. Discontinue PREZISTA/ritonavir immediately if signs or symptoms of severe skin reaction occur. These reactions cannot be excluded but are not limited to severe rash or rash accompanied with fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, hepatitis and/or eosinophilia. Rash (all grades, regardless of causality) occurred in 10.3% of subjects treated with PREZISTA/ritonavir [also see Adverse Reactions]. Rash was mostly mild-to-moderate, often occurring within the first four weeks of treatment and resolving with continued dosing. The discontinuation rate due to rash in subjects using PREZISTA/ritonavir was 0.5%.

Sulfa Allergy

Darunavir contains a sulfonamide moiety. PREZISTA should be used with caution in patients with a known sulfonamide allergy. In clinical studies with PREZISTA/ritonavir, the incidence and severity of rash was similar in subjects with or without a history of sulfonamide allergy.

Drug Interactions

See Table 1 for a listing of drugs that are contraindicated for use with PREZISTA/ritonavir due to potentially life-threatening adverse events, significant drug-drug interactions, or loss of therapeutic effect to PREZISTA [see Contraindications]. Please refer to Table 8 for established and other potentially significant drug-drug interactions [see Drug Interactions].

Diabetes Mellitus / Hyperglycemia

New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and hyperglycemia have been reported during postmarketing surveillance in HIV-infected patients receiving protease inhibitor (PI) therapy. Some patients required initiation or dose adjustments of insulin or oral hypoglycemic agents for treatment of these events. In some cases, diabetic ketoacidosis has occurred. In those patients who discontinued PI therapy, hyperglycemia persisted in some cases. Because these events have been reported voluntarily during clinical practice, estimates of frequency cannot be made and causal relationships between PI therapy and these events have not been established.

Fat Redistribution

Redistribution/accumulation of body fat, including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial edema, peripheral wasting, and “buffalo hump” have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

Immune Reconstitution Syndrome

During the initial phase of treatment, patients responding to antiretroviral therapy often develop an inflammatory response to indolent or residual opportunistic infections (such as Mycobacterium avium complex, cytomegalovirus, Pneumocystis jirovecii pneumonia, and tuberculosis), which may necessitate further evaluation and treatment.

Hemophilia

There have been reports of increased bleeding, including spontaneous skin hematomas and lymphedema in patients with hemophilia type A and B treated with PIs. In some patients, additional factor VIII was given. In more than half of the reported cases, treatment with PIs was continued or reintroduced if treatment had been discontinued. A causal relationship between PI therapy and these episodes has not been established.

Resistance/Cross-Resistance

Because the potential for HIV cross-resistance among PIs has not been fully explored in PREZISTA/ritonavir treated patients, the effect therapy with PREZISTA will have on the activity of subsequently administered PIs is unknown [see Microbiology (12.4) in full Prescribing Information].

ADVERSE REACTIONS

The overall safety profile of PREZISTA/ritonavir 800/100 mg once daily and PREZISTA/ritonavir 800/200 mg twice daily is based on clinical trials and post-marketing data, and is consistent with the data presented below.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Due to the need for co-administration of PREZISTA with ritonavir, please refer to ritonavir prescribing information for ritonavir-associated adverse reactions.

Clinical Trials Experience: Treatment-Naïve Adults

Study TMC14-C211

The safety assessment is based on data from the Phase 3 trial TMC14-C211 comparing PREZISTA/ritonavir 800/100 mg once daily versus lopinavir/ritonavir 800/200 mg per day in 689 antiretroviral treatment-naïve HIV-1 infected adult subjects. The total mean exposure for subjects in the PREZISTA/ritonavir 800/100 mg once daily arm and in the lopinavir/ritonavir 800/200 mg per day arm was 35.0 and 91.4 weeks, respectively.

The majority of the adverse drug reactions (ADRs) reported during treatment with PREZISTA/ritonavir 800/100 mg once daily were mild in severity. The most common clinical ADRs to PREZISTA/ritonavir 800/100 mg once daily (≥5%) of at least moderate intensity (≥ Grade 2) were diarrhea, headache, abdominal pain and rash. 2.3% of subjects in the PREZISTA/ritonavir arm discontinued treatment due to ADRs.

ADRs to PREZISTA/ritonavir 800/100 mg once daily of at least moderate intensity (≥ Grade 2) in antiretroviral treatment naïve HIV-1-infected adult subjects are presented in Table 2 and subsequent text below the table.

Table 2: Selected Clinical Adverse Drug Reactions to PREZISTA/ritonavir 800/100 mg Once Daily* of At Least Moderate Intensity (≥ Grade 2) Occurring in ≥ 2% of Antiretroviral Treatment-Naïve HIV-1-Infected Adult Subjects

<table>
<thead>
<tr>
<th>System Organ Class, Preferred Term</th>
<th>PREZISTA/ritonavir 800/100 mg once daily + TDF/FTC N = 343</th>
<th>lopinavir/ritonavir 800/200 mg per day + TDF/FTC N = 346</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>5%</td>
<td>6%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8%</td>
<td>15%</td>
</tr>
<tr>
<td>Nausea</td>
<td>3%</td>
<td>4%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2%</td>
<td>3%</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>&lt;1%</td>
<td>3%</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anorexia</td>
<td>2%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>6%</td>
<td>5%</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>5%</td>
<td>6%</td>
</tr>
</tbody>
</table>

N = total number of subjects per treatment group

TDF = tenofovir disoproxil fumarate
FTC = emtricitabine
* Excluding laboratory abnormalities reported as ADRs

Less Common Adverse Reactions

Treatment-emergent ADRs of at least moderate intensity (≥ Grade 2) occurring in less than 2% of antiretroviral treatment-naïve subjects receiving PREZISTA/ritonavir 800/100 mg once daily are listed below by body system:

Gastrointestinal Disorders: acute pancreatitis, dyspepsia, flatulence

General Disorders and Administration Site Conditions: anemia

Hepatobiliary Disorders: acute hepatitis (e.g., acute hepatitis, cytolytic hepatitis, hepatotoxicity)

Immune System Disorders: (drug) hypersensitivity

Metabolism and Nutrition Disorders: diabetes mellitus

Musculoskeletal and Connective Tissue Disorders: myalgia

Psychiatric Disorders: abnormal dreams

Skin and Subcutaneous Tissue Disorders: angioedema, pruritus, Stevens-Johnson syndrome, urticaria

Laboratory abnormalities: Selected Grade 2 to 4 for laboratory abnormalities that represent a worsening from baseline observed in antiretroviral treatment-naïve adult subjects treated with PREZISTA/ritonavir 800/100 mg once daily are presented in Table 3.
Table 3: Grade 2 to 4 Laboratory Abnormalities Observed in Antiretroviral Treatment-Naive HIV-1-Infected Adult Subjects

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-Density Lipoprotein Cholesterol</td>
<td>&gt; 3.0 to ≤ 5.0 X ULN</td>
<td>&gt; 5.0 to ≤ 10.0 X ULN</td>
<td>&gt; 10.0 X ULN</td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>&gt; 200 to ≤ 240 mg/dL</td>
<td>&gt; 240 to ≤ 300 mg/dL</td>
<td>&gt; 300 mg/dL</td>
</tr>
<tr>
<td>Elevated Glucose Levels</td>
<td>&gt; 275 mmol/L</td>
<td>&gt; 300 mg/dL</td>
<td>&gt; 350 mg/dL</td>
</tr>
<tr>
<td>Pancreatic Lipase</td>
<td>&gt; 1.5 to ≤ 3.0 X ULN</td>
<td>&gt; 3.0 to ≤ 5.0 X ULN</td>
<td>&gt; 5.0 X ULN</td>
</tr>
<tr>
<td>Pancreatic Amylase</td>
<td>&gt; 1.5 to ≤ 2.0 X ULN</td>
<td>&gt; 2.0 to ≤ 5.0 X ULN</td>
<td>&gt; 5.0 X ULN</td>
</tr>
</tbody>
</table>

Table 4: Selected Clinical Adverse Drug Reactions to PREZISTA/ritonavir 600/100 mg Twice Daily* of At Least Moderate Intensity (≥ Grade 2) Occurring in ≥ 2% of Antiretroviral Treatment-Experience HIV-1-Infected Adult Subjects

<table>
<thead>
<tr>
<th>System Organ Class, Preferred Term</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal Disorders</td>
<td>Abdominal distension</td>
<td>Abdominal pain</td>
<td>Diarrhea</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td>Anorexia</td>
<td>Diabetes mellitus</td>
<td>Nervous System Disorders</td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
<td>Headache</td>
<td>Rash</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Clinical Trials Experience: Treatment-Experience Adult Subjects

The safety assessment is based on all safety data from the Phase 3 trial TMC114-C214 comparing PREZISTA/ritonavir 600/100 mg twice daily versus lopinavir/ritonavir 400/100 mg twice daily in 592 antiretroviral treatment-experienced HIV-1-infected adult subjects. The total mean exposure for subjects in the PREZISTA/ritonavir 600/100 mg twice daily arm and in the lopinavir/ritonavir 400/100 mg twice daily arm was 80.7 and 76.4 weeks, respectively.

The majority of the ADRs reported during treatment with PREZISTA/ritonavir 600/100 mg twice daily were mild in severity. The most common clinical ADRs to PREZISTA/ritonavir 600/100 mg twice daily (≥ 5%) of at least moderate intensity (≥ Grade 2) were diarrhea, nausea, rash, abdominal pain and vomiting. 4.7% of subjects in the PREZISTA/ritonavir arm discontinued treatment due to ADRs.

ADRs to PREZISTA/ritonavir 600/100 mg twice daily of at least moderate intensity (≥ Grade 2) in antiretroviral treatment-experienced HIV-1-infected adult subjects are presented in Table 4 and subsequent text below the table.
Potential for Other Drugs to Affect Darunavir

Darunavir and ritonavir are metabolized by CYP3A. Drugs that induce CYP3A activity would be expected to increase the clearance of darunavir and ritonavir, resulting in lowered plasma concentrations of darunavir and ritonavir. Co-administration of darunavir and ritonavir and other drugs that inhibit CYP3A may decrease the clearance of darunavir and ritonavir and may result in increased plasma concentrations of darunavir and ritonavir (see Table 8).

Established and Other Potentially Significant Drug Interactions

Table 6 provides dosing recommendations as a result of drug interactions with PREZISTA/ritonavir. These recommendations are based on either drug interaction studies or predicted interactions due to the expected magnitude of interaction and potential for serious adverse events or loss of efficacy.

Table 6: Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction [See Clinical Pharmacology (12.3) in full Prescribing Information for Magnitude of Interaction, Tables 10 and 11]

<table>
<thead>
<tr>
<th>Concomitant Drug Name</th>
<th>Clinical Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maraviroc</td>
<td>Maraviroc concen.</td>
</tr>
<tr>
<td>digoxin</td>
<td>The lowest dose of digoxin should initially be prescribed. The serum digoxin concentrations should be monitored and used for titration of digoxin dose to obtain the desired clinical effect.</td>
</tr>
<tr>
<td>didanosine</td>
<td>Didanosine should be administered one hour before or two hours after PREZISTA/ritonavir (which are administered with food).</td>
</tr>
<tr>
<td>lopinavir/ritonavir</td>
<td>Appropriate doses of the combination have not been established. Hence, it is not recommended to co-administer lopinavir/ritonavir and PREZISTA, with or without ritonavir.</td>
</tr>
<tr>
<td>saquinavir</td>
<td>Appropriate doses of the combination have not been established. Hence, it is not recommended to co-administer saquinavir and PREZISTA, with or without ritonavir.</td>
</tr>
<tr>
<td>warfarin</td>
<td>The dose of warfarin should initially be prescribed. Caution is warranted and therapeutic concentration monitoring, if available, is recommended for anticoagulants when co-administered with PREZISTA/ritonavir.</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>Warfarin concen.</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>The dose of either darunavir/ritonavir or carbamazepine does not need to be adjusted when initiating co-administration with darunavir/ritonavir and carbamazepine. Clinical monitoring of carbamazepine concentrations and its dose titration is recommended to achieve the desired clinical response.</td>
</tr>
</tbody>
</table>

HIV-1-Antiviral Agents: Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

- didanosine ↔ darunavir ↔ didanosine
- lopinavir/ritonavir ↓ darunavir ↔ lopinavir
- saquinavir ↓ darunavir ↔ saquinavir

HIV-1-Antiviral Agents: HIV-Protease Inhibitors (PIs)

- indinavir (The reference regimen for indinavir was indinavir/ritonavir 800/100 mg twice daily.)
- didanosine ↔ darunavir ↔ didanosine
- lopinavir/ritonavir ↓ darunavir ↔ lopinavir
- saquinavir ↓ darunavir ↔ saquinavir

HIV-1-Antiviral Agents: CCR5 co-receptor antagonists

- Maraviroc ↑ maraviroc
- Maraviroc concentrations are increased when co-administered with PREZISTA/ritonavir. When used in combination with PREZISTA/ritonavir, the dose of maraviroc should be 150 mg twice daily.

Other Agents

- Antiarrhythmics: ↑ antiarrhythmics
- Contraindications of these drugs may be increased when co-administered with PREZISTA/ritonavir. Caution is warranted and therapeutic concentration monitoring, if available, is recommended for antiarrhythmics when co-administered with PREZISTA/ritonavir.
- digoxin ↑ digoxin

- Warfarin ↓ warfarin ↔ darunavir
- Warfarin concentrations are decreased when co-administered with PREZISTA/ritonavir. It is recommended that the international normalized ratio (INR) be monitored when warfarin is combined with PREZISTA/ritonavir.

- Carbamazepine ↔ carbamazepine
- The dose of either darunavir/ritonavir or carbamazepine does not need to be adjusted when initiating co-administration with darunavir/ritonavir and carbamazepine. Clinical monitoring of carbamazepine concentrations and its dose titration is recommended to achieve the desired clinical response.

- Phenobarbital, phenytoin ↓ ↔ phenobarbital, phenytoin
- Co-administration of PREZISTA/ritonavir may cause decrease in the steady-state concentrations of phenytoin and phenobarbital. Phenytoin and phenobarbital levels should be monitored when co-administering with PREZISTA/ritonavir.

Randomized Study TMC114-C214

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Preferred Term, Limit</th>
<th>BIOCHEMISTRY</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cholesterol</td>
<td>6.20-7.77 mmol/L</td>
<td>240-300 mg/dL</td>
<td>25%</td>
<td>23%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.13-4.50 mmol/L</td>
<td>180-190 mg/dL</td>
<td>14%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.91-5.1 mmol/L</td>
<td>191-196 mg/dL</td>
<td>8%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

N-normal; OBR-optimized background regimen; *Not applicable in Division of AIDS grading scale.
<table>
<thead>
<tr>
<th>Table 6: Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction [See Clinical Pharmacology (12.3) in full Prescribing Information for Magnitude of Interaction, Tables 10 and 11] (continued)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antidepressant:</strong> trazodone, desipramine</td>
</tr>
<tr>
<td><strong>Anti-inflammatory:</strong> colchicine</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Antifungals:</strong> ketoconazole, itraconazole, voriconazole</td>
</tr>
<tr>
<td><strong>Anti-gout:</strong> colchicine</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Antimycobacterial:</strong> rifabutin</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 6: Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction [See Clinical Pharmacology (12.3) in full Prescribing Information for Magnitude of Interaction, Tables 10 and 11] (continued)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>8-Blockers:</strong> metoprolol, timolol</td>
</tr>
<tr>
<td><strong>Benzodiazepines:</strong> midazolam</td>
</tr>
<tr>
<td><strong>Calcium Channel Blockers:</strong> calcium channel blockers</td>
</tr>
<tr>
<td><strong>Corticosteroid:</strong> dexamethasone</td>
</tr>
<tr>
<td><strong>Corticosteroid:</strong> fluticasone</td>
</tr>
<tr>
<td><strong>Endothelin receptor antagonists:</strong> bosentan</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>HMG-CoA Reductase Inhibitors:</strong> pravastatin, atorvastatin, rosvastatin</td>
</tr>
<tr>
<td><strong>Immunosuppressants:</strong> cyclosporine, tacrolimus, sirolimus</td>
</tr>
<tr>
<td><strong>Inhaled beta agonist:</strong> salmeterol</td>
</tr>
</tbody>
</table>
**Table 6: Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction** [See Clinical Pharmacology (12.3) in full Prescribing Information for Magnitude of Interaction, Tables 10 and 11](continued)

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Note</th>
<th>Interaction</th>
<th>Recommended Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Narcotic Analgesic/ Treatment of Opioid Dependence</td>
<td>methadone ↔ buprenorphine/naloxone, norbuprenorphine/metabolite</td>
<td>No adjustment of methadone dosage is required when initiating co-administration of PREZISTA/ritonavir. However, clinical monitoring is recommended as the dose of methadone during maintenance therapy may need to be adjusted in some patients. No dose adjustment for buprenorphine or buprenorphine/naloxone is required with concurrent administration of PREZISTA/ritonavir. Clinical monitoring is recommended if PREZISTA/ritonavir and buprenorphine or buprenorphine/naloxone are coadministered.</td>
<td>A dose decrease may be needed for these drugs when co-administered with PREZISTA/ritonavir.</td>
</tr>
<tr>
<td>Neuroleptics: risperidone, thioridazine</td>
<td>methylphenidate</td>
<td>Plasma concentrations of methylphenidate are decreased due to induction of its metabolism by ritonavir. Alternative methods of nonhormonal contraception are recommended.</td>
<td>Data are lacking on plasma concentrations of efavirenz, etravirine, nevirapine, omeprazole, ranitidine, and tenofovir disoproxil fumarate.</td>
</tr>
<tr>
<td>Oral Contraceptives/ Estrogens: ethinyl estradiol, norethindrone</td>
<td>ethinyl estradiol ↔ norethindrone</td>
<td>Plasma concentrations of ethinyl estradiol are decreased due to induction of its metabolism by ritonavir.</td>
<td>Plasma concentrations of ethinyl estradiol are decreased due to induction of its metabolism by ritonavir. Alternative methods of nonhormonal contraception are recommended.</td>
</tr>
<tr>
<td>PDE-5 inhibitors: sildenafil, vardenafil, tadalfil</td>
<td>PDE-5 inhibitors</td>
<td>Co-administration with PREZISTA/ritonavir may result in an increase in PDE-5 inhibitor-associated adverse events, including hypotension, syncope, visual disturbances and priapism. Use of PDE-5 inhibitors for pulmonary arterial hypertension (PAH): Use of sildenafil is contraindicated when used for the treatment of pulmonary arterial hypertension (PAH) [see Contraindications (4)]. The following dose adjustments are recommended for use of tadalfil with PREZISTA/ritonavir: Co-administration of tadalfil in patients on PREZISTA/ritonavir: In patients receiving PREZISTA/ritonavir for at least one week, start tadalfil at 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability. Co-administration of PREZISTA/ritonavir in patients on tadalfil: Avoid use of tadalfil during the initiation of PREZISTA/ritonavir. Stop tadalfil at least 24 hours prior to starting PREZISTA/ritonavir. After at least one week following the initiation of PREZISTA/ritonavir, resume tadalfil at 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability. Use of PDE-5 inhibitors for erectile dysfunction: Sildenafil at a single dose not exceeding 25 mg in 48 hours, vardenafil at a single dose not exceeding 2.5 mg dose in 72 hours, or tadalfil at a single dose not exceeding 10 mg dose in 72 hours can be used with increased monitoring for PDE-5 inhibitor-associated adverse events.</td>
<td>Data are lacking on plasma concentrations of efavirenz, etravirine, nevirapine, omeprazole, ranitidine, and tenofovir disoproxil fumarate.</td>
</tr>
</tbody>
</table>

Other nucleoside reverse transcriptase inhibitors (NRTIs): Based on the different elimination pathways of the other NRTIs (zidovudine, zalcitabine, emtricitabine, stavudine, lamivudine and abacavir) that are primarily excreted via the kidney, no drug interactions are expected for drugs other than PREZISTA/ritonavir.

Other PIs: The co-administration of PREZISTA/ritonavir and PIs other than lopinavir/ritonavir, saquinavir, atazanavir, and indinavir has not been studied. Therefore, such co-administration is not recommended.

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

Pregnancy Category C: PREZISTA should be used during pregnancy only if the potential benefit justifies the potential risk. No adequate and well-controlled studies have been conducted in pregnant women. Reproduction studies conducted with darunavir showed no embryotoxicity or teratogenicity in mice, rats and rabbits. However, due to limited bioavailability and/or dosage limitations, animal exposures (based on AUC) were only 50% (mice and rats) and 5% (rabbit) of those observed in humans. The recommended clinical dose boost with ritonavir was used in rats for co-administration of PREZISTA/ritonavir.

In the rat pre- and postnatal development study, a reduction in pup body weight was observed with darunavir alone or in combination with ritonavir during lactation. This was due to exposure of pups to drug substances via the milk. Sexual development, fertility and mating performance of offspring were not affected by maternal treatment with darunavir alone or in combination with ritonavir. The maximal plasma exposures achieved in rats were approximately 50% of those obtained in humans at the recommended clinical dose boosted with ritonavir.

In the juvenile toxicity study where rats were directly dosed with darunavir, darunavir-related adverse events were observed in a dose-dependent manner. However, an increase in body weight gain was observed with darunavir alone or in combination with ritonavir. The maximal plasma exposures achieved in rats were approximately 50% of those obtained in humans at the recommended clinical dose boosted with ritonavir.

**Antiretroviral Pregnancy Registry:** To monitor maternal-fetal outcomes of pregnant women exposed to PREZISTA, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register pregnant women by calling 1-800-258-4263.

**Nursing Mothers**

The Centers for Disease Control and Prevention recommend that HIV-infected mothers in the United States not breastfeed their infants to avoid risking postnatal transmission of HIV. Although it is not known whether darunavir is secreted in human milk, darunavir is not detected in the milk of lactating rats. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breastfeed if they are receiving PREZISTA.

**Geriatric Use**

Clinical studies of PREZISTA did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. In general, caution should be exercised in the administration and monitoring of PREZISTA in elderly patients reflecting the greater frequency of decreased hepatic function, and of concomitant disease or other drug therapy [see Clinical Pharmacology (12.3) in full Prescribing Information].

**Hepatic Impairment**

No dose adjustment of PREZISTA/ritonavir is necessary for patients with either mild or moderate hepatic impairment. No pharmacokinetic or safety data are available regarding the use of PREZISTA/ritonavir in subjects with severe hepatic impairment [see Contraindications (4)]. PREZISTA/ritonavir is not recommended for use in patients with severe hepatic impairment [see Dosage and Administration and Clinical Pharmacology (12.3) in full Prescribing Information].

**Renal Impairment**

Population pharmacokinetic analysis showed that the pharmacokinetics of darunavir were not significantly affected in HIV-infected subjects with moderate renal impairment (CrCL between 30-60 mL/min, n=20). No pharmacokinetic data are available in HIV-1-infected patients with severe renal impairment, end stage renal disease, or a creatinine clearance of darunavir is limited, a decrease in total body clearance is not expected in patients with renal impairment. Darunavir and ritonavir are highly bound to plasma proteins, it is unlikely that they will be significantly removed by hemodialysis or peritoneal dialysis [see Clinical Pharmacology (12.3) in full Prescribing Information].

**OVERDOSAGE**

Human experience of acute overdose with PREZISTA/ritonavir is limited. Single doses up to 3200 mg of the oral solution of darunavir alone and up to 1600 mg of the tablet formulation of darunavir in combination with ritonavir have been administered to healthy volunteers without untoward symptomatic effects.

No specific antidote is available for overdose with PREZISTA. Treatment of overdose with PREZISTA consists of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. If indicated, elimination of unabsorbed active substance is to be achieved by emesis or gastric lavage. Administration of activated charcoal may also be used to aid in removal of unabsorbed active substance. Since PREZISTA is highly protein bound, dialysis is unlikely to be beneficial in significant removal of the active substance.
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PA
tIENT COUNSELING INFORMATION

[See FDA-Approved Patient Labeling in full Prescribing Information]

A statement to patients and healthcare providers is included on the product's bottle label.

ALERT: Find out about medicines that should NOT be taken with PREZISTA®. A Patient Package Insert for PREZISTA® is available for patient information.

General

Patients should be informed that PREZISTA® is not a cure for HIV infection and that they may continue to develop opportunistic infections and other complications associated with HIV disease. Patients should be told that if they are currently not on a different treatment, therapy with PREZISTA® can reduce the risk of transmitting HIV to others.

Patients should be told that sustained decreases in plasma HIV RNA have been associated with a reduced risk of progression to AIDS and death. Patients should remain under the care of a physician while using PREZISTA®.

Instructions for Use

General

Patients should be advised to take PREZISTA® and ritonavir (NORVIR®) with food every day as prescribed. Patients should be instructed to swallow whole tablets with a drink such as water or milk. PREZISTA® must always be used with ritonavir (NORVIR®) in combination with other antiretroviral drugs.

Patients should be advised to report to their healthcare provider the use of any other prescribed or over-the-counter medication, herbal products, or dietary supplements.

PREZISTA/ritonavir may interact with many drugs; therefore, patients should be informed that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy, including PREZISTA/ritonavir, and that the cause and long-term health effects of these conditions are not known at this time.

Manufactured for Tibotec, Inc. by: JOLLIC, Gurabo, Puerto Rico

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BEST PRACTICES, continued from page 23

Dr. Jeffrey T. Kirchner, is medical director at Comprehensive Care Medicine for HIV Lancaster General Hospital Lancaster, PA, and is Chair of the HIV Specialist Editorial Advisory Group.

ways readily accepted. However, I think the data continues to become quite compelling, especially that from the 052 trial. I believe that when both the IAS and DHHS guidelines are updated serodiscordance will receive greater emphasis as a treatment indication.

To take this recommendation a step further, the question of condom use if the seropositive partner has an undetectable viral load once on treatment continues to be raised by patients.

In January 2008, the “Swiss Statement” was released stating that HIV-positive heterosexuals could stop using condoms with their regular HIV-negative partner if the following conditions were met: their partner agreed; they were taking HIV treatment; their blood viral load had been undetectable for at least six months, and they did not have any other sexually transmitted infections.

Although not supported by current prevention recommendations, I am aware that some of my patients have assumed this mindset—despite our counseling that condom use is still recommended.

What is the risk of not using a condom with a presumed undetectable viral load? The absolute answer to this question is not known. However, it could be significant, based on a recent presentation by Genberg (MACH-14 Study) who found that viral load begins to increase by 25 percent after just two to six days of missed therapy with further increases noted between days 14 and 21. Even a few missed doses of medication could have significant implications for HIV transmission.

So for now, I believe prudent advice to our patients in serodiscordant relationships is that there is very good evidence that treatment will “protect” their partner from HIV infection, but condoms should still be a standard part of safe-sex counseling and practice.

ABOUT THE AUTHOR:

Dr. Jeffrey T. Kirchner, is medical director at Comprehensive Care Medicine for HIV Lancaster General Hospital Lancaster, PA, and is Chair of the HIV Specialist Editorial Advisory Group.

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Federal Debt Limit & Budget Agreement

After months of proposals, bargaining and standoffs by Congressional Republicans and Democrats and the White House, an agreement on the federal debt limit, budget, and deficit reduction was reached in early August. At best, this agreement may affect funding for many HIV programs in the near future. At worst, it could ultimately impact some providers’ bottom line.

How does the federal debt limit impact funding for HIV? It does not, directly. The federal debt is a measure of the financial obligations of the U.S. federal government. Congress has constitutional authority to borrow money on the credit of the United States, and the country has had a public debt since its founding. During World War 1, Congress established an aggregate limit, or “ceiling,” on the total amount of debt that could be accumulated.

Congress has regularly raised this amount to avoid devaluation of the country’s international credit by bumping up against the limit. However, the debt ceiling is usually raised in concert with passage of a Congressional budget. During the course of negotiating a debt limit increase this year, Congressional Republicans insisted that the debt ceiling should not be raised unless accompanied by significant cuts to federal spending. Since many HIV related programs and services are financed through federal spending, cuts in federal spending are potential threats to HIV programs such as the Ryan White program, ADAP, Medicare and Medicaid, and research at NIH.

On Monday, August 2, 2011 (just days before the debt limit was due to be reached) the House of Representatives passed the “Budget Control Act” by a vote of 269-161. The next day the Senate passed the same bill by a vote of 74-26, and the President signed it into law. The final agreement raises the debt ceiling by $2.4 trillion through 2012 and cuts an additional $2.3 - $2.5 trillion in federal spending over 10 years, in two stages.

The first stage involves approximately $900 billion in agreed-upon cuts over the next 10 years (enforced by binding annual caps through 2021). About $25 billion of those cuts are set to take place in the next fiscal year. For non-security discretionary funding (which includes HHS, CDC, HRSA, SAMHSA and NIH), the law provides nearly $15 billion less in funding for fiscal year (FY) 2012, than Congress provided in FY11. This translates to a 4% cut from current funding levels. Since Congress has not yet marked up the appropriations bills for health agencies, it is unclear exactly which programmatic budgets will be reduced. HIV programs at all federal agencies may face cuts in funding, as will many other federal programs.

The second stage is an additional $1.5 trillion in reductions to be determined by a 12 member joint congressional committee. This committee (composed of 3 Democrats and 3 Republicans from each chamber) will make recommendations for further savings for Congress to consider—probably including cuts to both discretionary and defense programs, changes to entitlement programs like Medicare, and also new tax reforms and initiatives. Nothing is off the table for the committee in terms of considerations to lower the deficit.

As an enforcement mechanism, if Congress fails to pass a proposal from the committee that cuts the deficit by at least $1.2 trillion, automatic across-the-board cuts in spending will kick in (a process called sequestration) totaling that amount. The sequestration cuts will come from half national security and defense budgets, and half non-defense discretionary programs.

The Medicaid and Social Security programs for low-income individuals are exempted from the automatic across the board cuts. However, Medicare will face reductions, limited to no more than 2 percent, which are restricted to the provider side of the program, and not to beneficiaries. Therefore, under this agreement, automatic cuts to the Medicare program would affect provider reimbursement. Sequestration would take effect in January of 2013 -- but only if Congress does not pass some other measure to cut the deficit first.

One silver lining of the debt limit agreement is that it may diffuse some of the potential for intense budget showdowns in Congress. The compromise, in effect, functions as budget resolution for the next two years, and effectively sets top-line spending levels for both FY 2012 and FY 2013.

While appropriators must still reach agreement on how to distribute spending amounts to meet these targets, this legislation should ease the prospects of the type of budget standoff that led to this spring’s government shutdown drama. For federal grant recipients, like Ryan White providers, this measure should protect them from receiving the partial funding amounts in spurts that were seen this year as a result of short-term continuing resolutions.
eRX – The Future of Prescribing?
Here’s a primer to help you get started

**HIV Providers are encouraged** to begin participating in the U.S. government’s new electronic prescribing, or E-prescribing (eRx), program in order to take advantage of Medicare payment incentives and avoid penalties.

E-prescribing is a computer-based way to generate prescriptions through an automated data-entry process. Prescriptions are generated by using e-prescribing software and transmitted through a cyber-network to participating pharmacies in an effort to improve patient safety, streamline communication with pharmacists, and reduce medication costs.

In addition to diminishing the risk of medication errors and decreasing liability risks, e-prescribing systems will provide medication management through drug utilization review (DUR) programs and give the healthcare professional access to the patient’s most up-to-date medical history. This check and balance system helps to safeguard against improper dosage distribution, adverse reactions, drug contraindications, and will alert the provider if interactions are found. E-prescriptions can also help to reduce phone calls and call-backs to pharmacies and transmitting patient information via fax.

E-prescriptions may also increase patient compliance by streamlining refill requests and authorization processes.

**What does it mean for my practice?**
The Medicare Modernization Act (MMA) of 2003 initiated the move towards e-prescribing with a Voluntary Prescription Drug Benefit Program that required that an eRx program be established, and in 2008, the Medicare Improvements for Patients and Providers Act (MIPPA) authorized a new incentive program for eligible professionals who are successful electronic prescribers.

There is no sign-up or pre-registration for participation in the eRx Incentive Program, but there are limitations for who can qualify for an eRx incentive payment. First, an eligible professional must have and use a qualified eRx system and report on its adoption and use. Second, the eligible professional must meet the criteria for successful electronic prescriber specified by CMS for a particular reporting period. Finally, at least 10 percent of a successful electronic prescriber’s Medicare Part B covered services must be made up of codes that appear in the denominator of the eRx measure.

For 2011 and 2012, eligible professionals who are successful electronic prescribers may qualify to earn an incentive payment equal to 1.0 percent of the total estimated allowed charges submitted not later than two months after the end of the reporting period. For 2013, the incentive payment amount is reduced to 0.5 percent.

Beginning in 2012, eligible healthcare professionals who are not successful electronic prescribers may be subject to lesser payments or a penalty. The MIPPA requires CMS to subject eligible professionals who are not successful electronic prescribers under the eRx Incentive Program to a payment adjustment, starting in 2012. This adjustment applies to all of the eligible professional’s Part B-covered professional services under the Medicare Physician Fee Schedule (MPFS). From 2012 through 2014, the payment adjustment will increase with each new reporting period.
On May 28th, 2011, The Center for Medicare and Medicaid Services (CMS) announced it would be more flexible in allowing doctors to phase in e-prescribing technology. Providers who fail to complete at least 10 paperless prescriptions using an approved e-prescribing system between January 1 and June 30, 2011 will receive a 1 percent cut in Medicare reimbursements in 2012, a 1.5 percent cut in 2013 and a 2 percent cut in 2014. However, CMS states that physicians can choose from several reasons for not complying, such as limiting prescribing activity during the six month time frame or residing in an area where regulations hinder e-prescribing. Nevertheless, CMS is not retreating from its commitment to a paperless operation, although it understands that it may take more time for providers to adjust to the new system.

It is not too late to start participating in the 2010 Electronic Prescribing Incentive Program and potentially qualify to receive a full-year incentive payment for 2011. To become a certified electronic prescriber for the purpose of avoiding the 2012 eRx payment adjustment, eligible professionals must report the eRx measure for a minimum number of unique eRx events between January 1, 2011 and June 30, 2011. Eligible professionals may begin reporting the eRx measure at any time throughout the 2011 program year of January 1 through December 31, 2011 to be incentive eligible, but must have done so before June 30, 2011 to be exempt from the 2012 payment adjustment.

**Am I an eligible professional?**

Eligible professionals must have prescribing authority in order to participate in this program. The following professionals are eligible:

1. Medicare physicians (Doctors of Medicine, Osteopathy, Podiatric Medicine, Optometry, Oral Surgery, Dental Medicine, Chiropractic),
2. Practitioners (Physician Assistant, Nurse Practitioner, Clinical Nurse Specialists, Certified Registered Nurse Anesthetist, Certified Nurse Midwife, Clinical Social Worker, Clinical Psychologist, Registered Dietitian, Nutrition Professional, Audiologists),
3. Therapists (Physical Therapist, Occupational Therapist, Qualified Speech-Language Therapists.

**What does my practice need to get started e-prescribing?**

1. Decide whether you wish to choose stand-alone e-prescription software or a full electronic medical record (EMR) system that includes e-prescribing functionality. (A stand alone system is less costly, less complex, and faster to implement; however not all stand-alone e-prescribing systems include other patient medical history information, which could impact a prescriber’s medication decisions.)
2. Choose an e-prescription software vendor that utilizes a company that supplies the electronic prescribing network hub or gateway.
3. Install an internet connection (preferably high speed).
4. Purchase hardware such as a desktop PC, laptop, pocket PC’s, table PC’s, PDA’s utilizing a wire or wireless network.

For more resources on eRX, visit the Academy’s website at [www.aahivm.org](http://www.aahivm.org).
A S ROME, THE ETERNAL CITY, played host to the 6th International AIDS Society meeting in mid-July, it was only fitting the conference should make history. Thousands of attendees listened in rapt silence to presentations of sentinel prevention trials - the first large trials to broadly support antiretroviral therapy as a way to prevent HIV in heterosexuals, the populations most affected by HIV worldwide.

HPTN 052 examined virologically linked HIV transmission in 1,763 HIV-infected, sexually active serodiscordant couples with the CD4 count of the infected partner in the 350-550 range. 886 couples initiated ART at CD4 350-550 (immediate) vs. 877 at CD4 <250 (delayed). All received intensive risk reduction/condom counseling. A 96 percent reduction was seen in these serodiscordant couples with four transmissions in the immediate arm and 35 in the delayed. Of the 28 linked transmissions, only one occurred in the immediate arm and is believed to have occurred close to therapy initiation, prior to virologic suppression. Immediate therapy also resulted in a 41 percent reduction in HIV-related clinical events, with excess events in the delayed arm driven primarily by TB, specially extrapulmonary.

Partners PrEP followed 4,747 HIV-serodiscordant heterosexual couples for 36 months randomized 1:1:1: Tenofovir disoproxil fumarate (TDF) vs. TDF/ FTC vs. placebo. Both PrEP regimens significantly reduced HIV transmission vs. placebo in both men and women (Efficacy- TDF 55 percent men/68 percent women and TDF/ FTC 83 percent men/62 percent women) with no significant difference in efficacy of TDF vs. TDF/FTC in reducing HIV acquisition. Both regimens were well tolerated with reported unprotected sex decreased across all arms.

TDF2 looked at TDF/FTC vs. placebo in 1219 heterosexually active HIV-uninfected adults aged 18-39 years of age followed for at least 12 months. Overall protective efficacy of TDF/FTC was 62.6 percent with nine vs. 24 patients seroconverting. While reduction in HIV acquisition occurred in both sexes, the study was underpowered to demonstrate gender-based outcomes differences.

**Treatment Strategies**

Some interesting new treatment strategies also were presented, with integrase inhibitors taking center stage. SPRING-1, a large phase II naïve trial, studied three doses of QD dolutegravir (DTG) vs. efavirenz (EFV) with ABC/3TC or TDF/FTC backbone. While viral load fell faster in all DGV arms, week 48 response rates were only modestly better than EFV (88-91 percent in the three DGV arms vs. 82 percent in EFV arm). No integrase mutations were detected in patients failing DTG through 48 weeks with fewer adverse events in the DTG arms. Forty-eight week results of the QD integrase inhibitor elvitegravir (EVG) vs. BID raltegravir (RGT) in ART experienced patients were encouraging. The trial added study medication and placebo to a boosted PI and third active agent backbone. EVG proved noninferior with TLOVR (HIV-1 RNA <50 copies) 59 vs. 58 percent. Similar rates of virologic failure and adverse events were seen with both though numerically greater integrase resistance mutations at failure were seen with EVG.

Pooled ECHO/THRIVE 96 week data was presented with identical efficacy (77.6% with HIV RNA<50 copies). While more virologic failures occurred with the NNRTI rilpivirine than efavirenz (14.0 vs. 7.6 percent), more discontinuations for adverse events occurred with EFV than RPV (8.5 vs. 4.1 percent).

Two significant maraviroc studies were presented. In a study pitting maraviroc vs. TDF/FTC with a backbone of ATV/rtv in naïve patients, only 74.6 percent of those on MVC vs. 83.6 percent of those receiving TDF/FTC had HIV RNA<50 at 48 weeks. CD4 increases were similar, although grade three/four adverse events (especially hyperbilirubinemia) were more common on MVC. Interestingly a post hoc analysis of the 448 patients in MOTIVATE who received
MVC QD vs. BID vs. placebo (all with a boosted PI regimen) showed similar efficacy in those receiving MVC (45.5 percent vs. 47.7 percent with HIV RNA < 50 copies).9

SPARTAC readdressed the issue of treatment for primary infection. Here, 372 patients diagnosed within six months of infection were randomized to a limited course of ART for 12 vs. 48 weeks vs. SOC (no immediate ART). HR for ART12 vs. SOC was 0.93 and for ART 48 vs. ART 12-0.68. If therapy was started within 12 weeks of conversion in the ART48 arm, HR decreased to 0.48. HIV-RNA set point was 0.44 log10 copies/ml lower in the ART48 arm vs. SOC at 36 weeks after the treatment ended with higher CD4 counts in long term follow-up.10

Complications
Treatment complications were addressed in a number of large trials. The VA database was analyzed for osteoporotic fractures occurring from 1988-2009. Cumulative use of TDF/and/or a boosted PI was associated with a higher risk—especially concomitant use.11 2693 patients with CrCl> 60 ml/min in the French Aquitaine Cohort were followed from 2004-2008, with 86 cases of incident CKD observed. Of these, 96 percent had a baseline CrCl< 90 and 90 percent had >/= 3 traditional risk factors (female sex, older age, diabetes, hyperlipidemia, pre-existing mild renal dysfunction and low CD4 count). Risk ratio for TDF use adjusted for other risk factors in multivariate analysis was 2.5. With at least six months of concomitant PI therapy, that rose to 3.5.12

Several fascinating symposia were held on inflammation and aging. The most thought provoking one that I attended was given by Dr. William Powderly. He argued we are too quick to get on the “premature aging in HIV” bandwagon. He feels substance abuse, including tobacco, co-morbidities such as HCV, and socioeconomic factors are probably more important players, although perhaps chronic viremia and inflammation play a role. He suggests we start comparing our patients to controls well matched for the above.

Like all good conferences, IAS 2011 left us looking to the future and filled with more questions than answers. Is ART as prevention possible in a world where we can’t even fund treatment for those already infected, even in a wealthy country like the US? How do we best use the available ART agents to prevent resistance and toxicity? What is the real relationship between HIV and inflammation, ART and aging? Stay tuned ... more to come in DC in 2012.

References:

GILEAD PIPELINE UPDATE continued from page 21

References
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